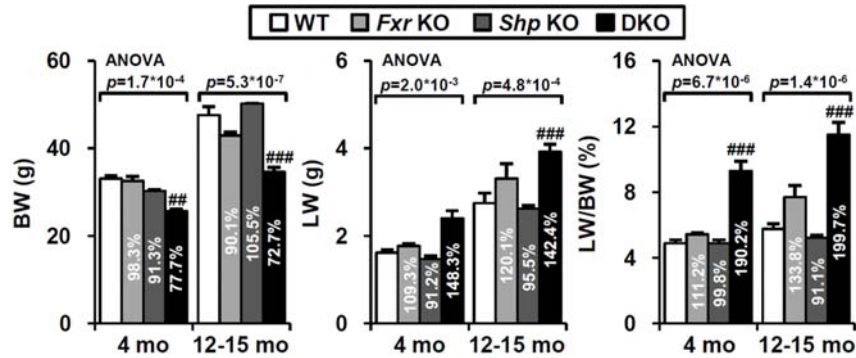
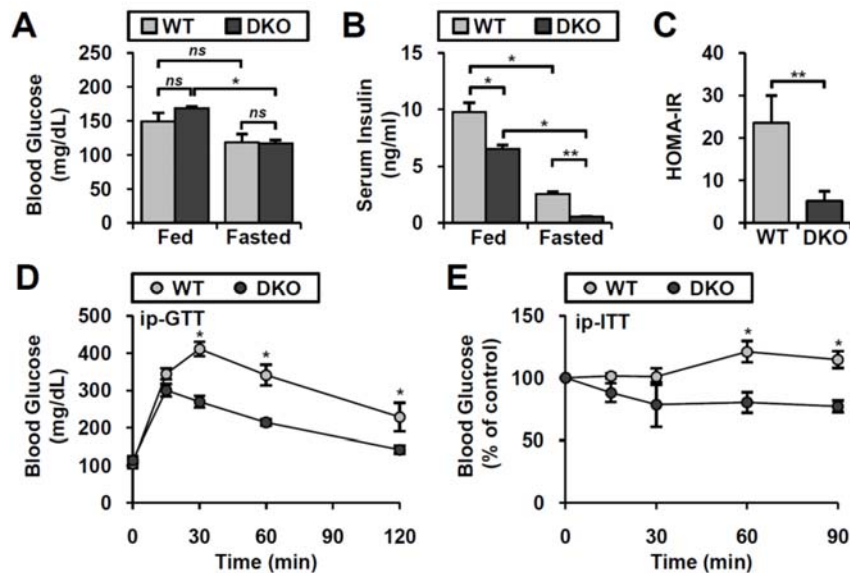


Supporting Figures

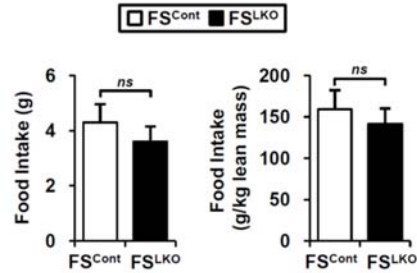


Supporting Fig. S1. Significant body weight changes in aged DKO mice. (A) Body weight, (B) liver weight and (C) liver/body weight ratio of *Fxr* single knockout, *Shp* single knockout and DKO were calculated at 4 month and 12-15 month old age (n=3~10). Numerical values in bar graphs indicate relative percentage compared to WT (%). One-way ANOVA followed by post hoc t-test. ###p<0.0017, ####p<0.00083 compared to WT.

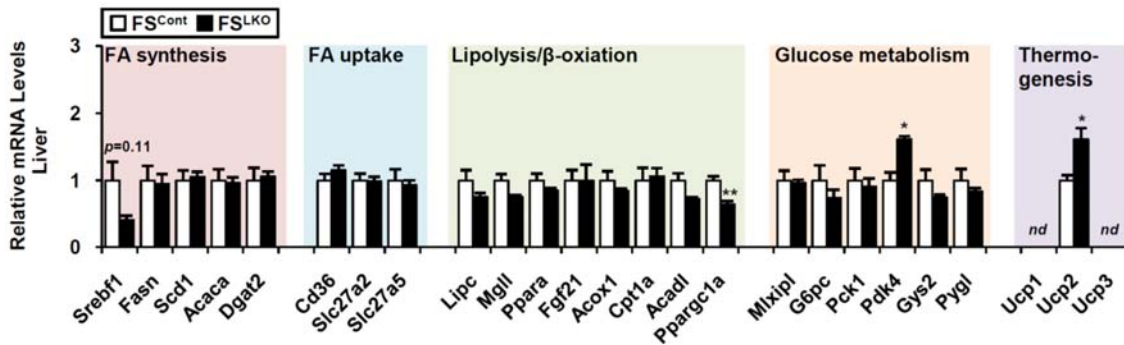


Supporting Fig. S2. Improved glucose metabolism in DKO mice. Feeding and fasting (A) blood glucose and (B) serum insulin levels of 1 year old DKO were measured (n=2~3). (C) HOMA-IR index of DKO mice. (D) GTT and (E) ITT of DKO mice at 1 year old age

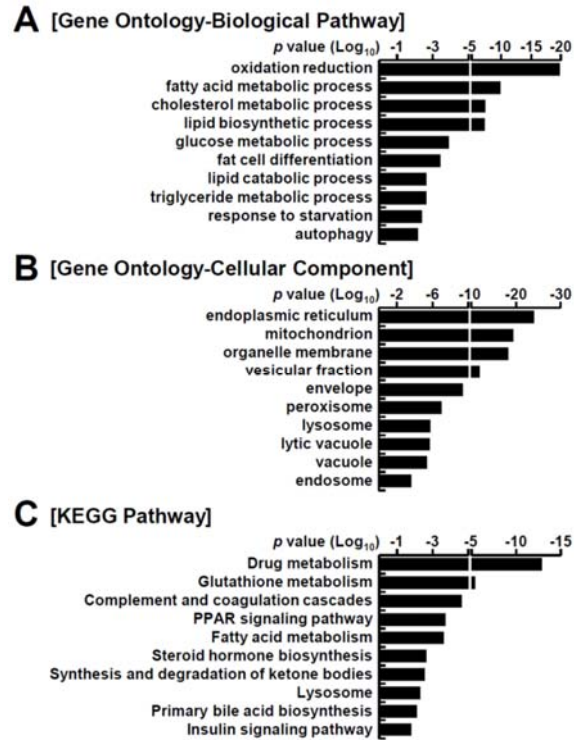
(n=2~3). *ns*, not significant. Student's t-test, * $p < 0.05$, ** $p < 0.01$.



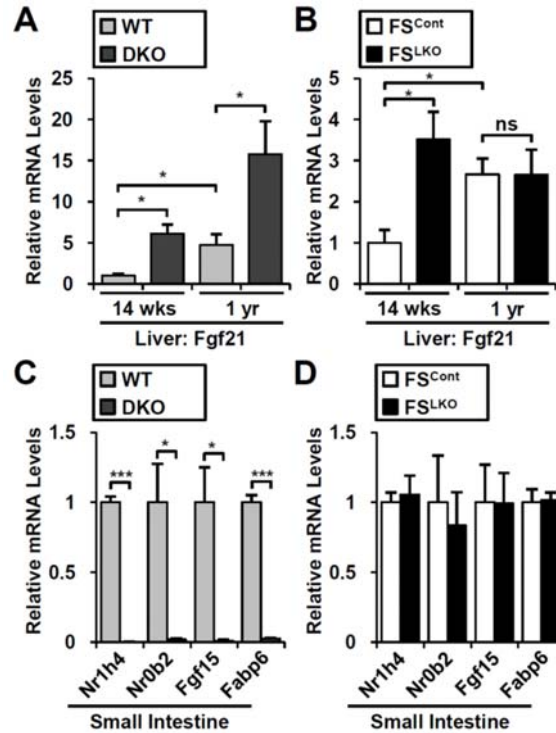
Supporting Fig. S3. Unchanged food intake in FSLKO mice. Daily food intake was measured (n=3). In the right panel, the absolute amount from the left panel was normalized to lean mass. *ns*, not significant.



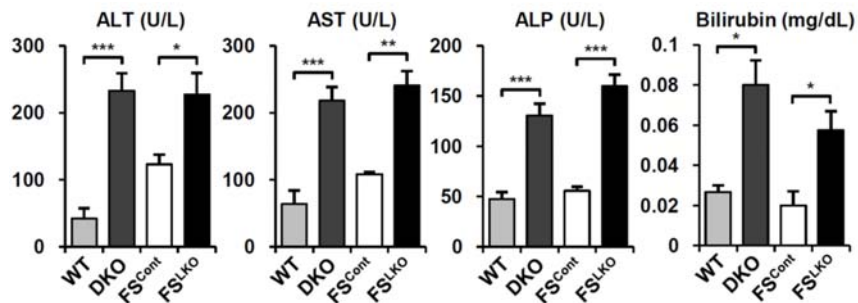
Supporting Fig. S4. Hepatic fatty acid/glucose metabolism gene expressions in FSLKO. Gene expression involved in fatty acid synthesis, fatty acid uptake, lipolysis, β-oxidation, glucose metabolism and thermogenesis were analyzed by qPCR (n=4). *nd*, not detected. Student's t-test, * $p < 0.05$, ** $p < 0.01$.



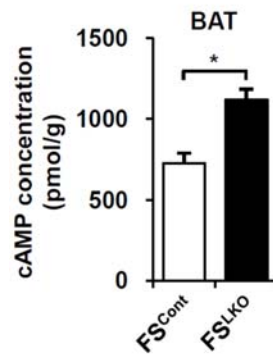
Supporting Fig. S5. Gene ontology and KEGG pathway analysis of altered gene lists in DKO microarray. Genes showing differential expression in DKO microarray ($p < 0.01$) were analyzed using DAVID Tools. Initially, 192 biological pathways (GO-BP), 62 cellular components (GO-CC) and 20 KEGG pathways were identified ($p < 0.01$) (Supporting Table S3-5). Then, these gene sets were further classified into several functional/locational categories and representative results are shown in (A) biological pathway, (B) cellular component and (C) KEGG pathway.



Supporting Fig. S6. The hepatic *Fgf21* and intestinal *Fgf15* expression in DKO and FS^{LKO} liver. Hepatic *Fgf21* expression was determined by Q-PCR in (A) DKO and (B) FS^{LKO} mice at 14 weeks and 1 yr old age. The intestinal *Fgf15* expression was analyzed in ileum of (C) DKO and (D) FS^{LKO} mice at 14 weeks old age.



Supporting Fig. S7. Liver injury in aged DKO and FS^{LKO} mice. Serum ALT, AST, ALP and bilirubin levels were analyzed in 1 year old DKO and FS^{LKO} mice.



Supporting Fig. S8. Increased cAMP levels in F5^{LKO} BAT. cAMP level was measured in BAT extract according to the manufacturer's protocol (Direct cAMP ELISA Kit, ENZO Life Sciences, #ADI-900-066).

Supporting tables

Supporting Table S1. Primer sequences used for Q-PCR

Gene Symbol	Forward primer	Reverse primer
Abcb11 (Bsep)	GCTGCCAAGGATGCTAATGC	CTACCCTTGCTTCTGCCCA
Acaca	CATGCGATCTATCCGTCGGT	CCTCCAGGCACTGGAACATAG
Acadl	GCGATTTCTGCCTGTGAGTTC	ACCGTCTGTATGTGTGCAACT
Acox1	GAGCCTTTGGACCTTCACTTGG	CGCATAAGTGCCCGTGATCT
Acs11	ACCAGCCCTATGAGTGGATTT	CAAGGCTTGAACCCCTTCTG
Acs14	TCCTCCAAGTAGACCAACCCC	AGTCCAGGGATACGTTACACAC
Agpat9	CGGATTATCCCTGGGTATCTCG	CGAAGTCCCTTCCCTCGAAGAC
Atg7	TGCCTATGATGATCTGTGTC	CACCAACTGTTATCTTTGTCC
Atg12	GGCCTCGGAACAGTTGTTTA	CAGCACCGAAATGTCTCTGA
Atg16l1	CGAATCTGGACTGTGGATGA	AGCAGGAACTTGGCAGAGAG
Dgat2	AGTGGCAATGCTATCATCATCGT	AAGGAATAAGTGGGAACCAGA
Dio2	AGGATGCACACGGAAAGGAG	ACCTATCTTTGCCATCGCCC
Cd36	GCCAAGCTATTGCGACATGAT	CAGATCCGAACACAGCGTAGA
Cidea	CATACATCCAGCTCGCCCTT	CGTAACCAGGCCAGTTGTGA
Cpt1a	GGACTCCGCTCGCTCATTC	GAGATCGATGCCATCAGGGG
Ctsd	CTGGCTCCTCTAACCTGTGG	GACGTGCCGTTCTTACATA
Elovl1	CCGGCCCTGATCCCTTTG	AGCTCGTGGTACAAGTTCACA
Elovl2	TACCCTGGACAGCGCATCG	CACCCGCGAACTCGAGAAT
Elovl3	GAGGCACACACAAACACTCAAT	AGGACTTGTTCCTACTGTTCTT
Elovl5	GCAGCTTGCTTCTGTTCCCG	GAGTGACGCATCGAAATGTTCC
Elovl6	CCTTCTGGGTGAGGACTCG	CCGTCCACTAATCTCTGCC
Fabp6 (IBabp)	CAAGGCTACCGTGAAGATGGA	CTTACGCGCTCATAGGTCACA
Fads1	AGCACATGCCATACAACCATC	TTTCCGCTGAACCACAAAATAGA
Fads2	GATGGCTGCAACATGACTATGG	GCTGAGGCACCCTTAAGTGG
Fasn	AAGCAGGCACACACAATGGA	AGTGTTCGTTCCCTCGGAGTG
Fgf21	ATCAGGGAGGATGGAACAGTGG	AGCTCCATCTGGCTGTTGGCAA
Fgf15	AGGAGGACCAAAAACGAACGAA	GAGTAGCGAATCAGCCCCTAT
G6pc	TGCTGTGTCTGGTAGGCAAC	AACATCGGAGTGACCTTTGG
Gapdh	CTTTGGCATTGTGGAAGGGC	CAGGGATGATGTTCTGGGCA
Gpat4	AAAAGCAAGCTGCCCATCCT	AGAAGGCGTCACCAAACCTGA
Gys2	GCAGTGATGCGGAAGACGAA	AGTGGTTCAGAGAAAACGGTGA
Lipe (Hsl)	AATGAGATGGCGAGGGTCCAG	GCCCTCACAGCAGGAATAGT
Lipc	TGAGGCCAGAGACATGGG	CAAGGCTTCTCCCAAAGGGC
Mgl1	CGCGCAGTAGTCTGGCTCTA	ATTCTGTGGAGTTCGCCTGG
Mlxipl (Chrebp)	AGAAGAGATCAGGGCAAGGG	CCAACCCTGCAGACAGTTTT
Nr1h4 (Fxr)	TCCGGACATTCAACCATCAC	TCACTGCACATCCCAGATCTC
Nr0b2 (Shp)	CGATCCTCTTCAACCCAGATG	AGGGCTCCAAGACTTCACACA
Pdk4	AGATTGACATCCTGCCTGACC	TCTGGTCTTCTGGGCTCTTCT
Pck1	TGCGGATCATGACTCGGATG	AGGCCAGTTGTTGACAAA
Pnpla2 (Atgl)	CCTTAGGAGGAATGCCCTGC	CTCCAGCGGCAGAGTATAGG
Ppara	ACAAGGCCTCAGGTTACCA	GCCGAAAGAAGCCCTTACAG
Ppargc1a	ATGTGTCGCCTTCTTGTCT	ATCTACTGCCTGGGGACCTT
Prdm16	GGAGGAGGAGAGAGATTCCG	AGGTCCGGGTCAGGTTACATAC
Pygl	GCATGGAAACCCTTGGGAGA	CGTCTGGGTGTGCTCTACTC
Scd1	GCGATACTACTCTGGTGTCTCA	CCCAGGGAAACCAGGATATT
Scd2	TGGAGACGGAAGCTGCAAGA	AACAGTAAGCCTCTGCCAAGC
Slc27a2 (Fatp2)	ATCGTGGTTGGGGCTACTTTAG	TTTGGTTTCTGCGGTGTGTTG

Slc27a5 (Fatp5)	GAGGGCAATGTGGGCTTAATG	AGGCTCTGCTGTCTCTATGTC
Srebf1	GGGCAAGTACACAGGAGGAC	AGATCTCTGCCAGTGTGTC
Sqstm1	AGGAACAGATGGAGTCGGGA	CTAGAGAGCTTGCCCTTCC
Ucp1	GGATGGTGAACCCGACAAC	GCTGAAACTCCGGCTGAGAA
Ucp2	TCTGCACTCCTGTGTTCTCT	TAGAAAATGGCTGGGAGACGA
Ucp3	GACTCCGCCCTCTGTAATG	CAGATCACGCTCCATCCTCC

Supporting Table S2. Primer sequences used for ChIP-PCR

Gene Symbol	Forward primer	Reverse primer
Atg7_1 ChIP	AGTTGAGCGGCGGTAAGTAA	GAGTACGAGGGGACCCGAGTA
Atg7_2 ChIP	TCATCTGCCTGGAACATCTGTC	TGAACCTTGATCCTGTGGTTTTGT
Atg12 ChIP	GGAGGTGGGACTGGGATTAAC	ATAGCGCTCCATACTCGGTT

Supporting Table S3. DAVID Analysis of Gene Ontology (Biological Pathways)

Category	Term	RT	Count	%	P-Value	Benjamini
GOTERM_BP_FAT	oxidation reduction	RT	182	6.9	1.60E-20	6.10E-17
GOTERM_BP_FAT	fatty acid metabolic process	RT	60	2.3	1.50E-10	2.90E-07
GOTERM_BP_FAT	cofactor metabolic process	RT	58	2.2	8.30E-10	1.10E-06
GOTERM_BP_FAT	sterol metabolic process	RT	33	1.2	2.00E-09	1.90E-06
GOTERM_BP_FAT	steroid metabolic process	RT	52	2	4.10E-09	3.20E-06
GOTERM_BP_FAT	coenzyme metabolic process	RT	48	1.8	4.40E-09	2.90E-06
GOTERM_BP_FAT	cholesterol metabolic process	RT	29	1.1	5.50E-08	3.00E-05
GOTERM_BP_FAT	lipid biosynthetic process	RT	74	2.8	6.70E-08	3.30E-05
GOTERM_BP_FAT	adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	RT	32	1.2	9.80E-08	4.20E-05
GOTERM_BP_FAT	adaptive immune response	RT	32	1.2	9.80E-08	4.20E-05
GOTERM_BP_FAT	secondary metabolic process	RT	28	1.1	1.60E-07	6.20E-05
GOTERM_BP_FAT	organic acid biosynthetic process	RT	43	1.6	6.20E-07	2.80E-04
GOTERM_BP_FAT	carboxylic acid biosynthetic process	RT	43	1.6	6.20E-07	2.20E-04
GOTERM_BP_FAT	vitamin metabolic process	RT	27	1	6.50E-07	2.10E-04
GOTERM_BP_FAT	monosaccharide metabolic process	RT	53	2	7.10E-07	2.10E-04
GOTERM_BP_FAT	heterocycle catabolic process	RT	21	0.8	8.90E-07	2.50E-04
GOTERM_BP_FAT	response to wounding	RT	82	3.1	9.00E-07	2.30E-04
GOTERM_BP_FAT	steroid biosynthetic process	RT	27	1	1.20E-06	3.00E-04
GOTERM_BP_FAT	hexose metabolic process	RT	48	1.8	1.20E-06	2.80E-04
GOTERM_BP_FAT	lymphocyte mediated immunity	RT	28	1.1	1.50E-06	3.30E-04
GOTERM_BP_FAT	regulation of cell adhesion	RT	32	1.2	1.70E-06	3.40E-04
GOTERM_BP_FAT	acute inflammatory response	RT	29	1.1	1.90E-06	3.60E-04
GOTERM_BP_FAT	cellular amino acid biosynthetic process	RT	20	0.8	1.90E-06	3.50E-04
GOTERM_BP_FAT	sterol biosynthetic process	RT	16	0.6	2.40E-06	4.30E-04
GOTERM_BP_FAT	isoprenoid metabolic process	RT	21	0.8	3.00E-06	5.00E-04
GOTERM_BP_FAT	positive regulation of immune system process	RT	54	2	3.60E-06	5.80E-04
GOTERM_BP_FAT	diterpenoid metabolic process	RT	15	0.6	5.30E-06	8.20E-04
GOTERM_BP_FAT	retinoid metabolic process	RT	15	0.6	5.30E-06	8.20E-04
GOTERM_BP_FAT	vitamin biosynthetic process	RT	15	0.6	8.90E-06	1.30E-03
GOTERM_BP_FAT	terpenoid metabolic process	RT	15	0.6	8.90E-06	1.30E-03
GOTERM_BP_FAT	protein maturation by peptide bond cleavage	RT	24	0.9	9.80E-06	1.40E-03
GOTERM_BP_FAT	vitamin A metabolic process	RT	14	0.5	1.20E-05	1.60E-03
GOTERM_BP_FAT	leukocyte mediated immunity	RT	29	1.1	1.50E-05	1.90E-03
GOTERM_BP_FAT	fat-soluble vitamin metabolic process	RT	16	0.6	1.70E-05	2.20E-03
GOTERM_BP_FAT	retinoic acid metabolic process	RT	11	0.4	1.90E-05	2.40E-03
GOTERM_BP_FAT	immunoglobulin mediated immune response	RT	23	0.9	1.90E-05	2.30E-03
GOTERM_BP_FAT	positive regulation of immune response	RT	38	1.4	2.80E-05	3.20E-03
GOTERM_BP_FAT	antigen processing and presentation of exogenous antigen	RT	14	0.5	3.20E-05	3.60E-03
GOTERM_BP_FAT	B cell mediated immunity	RT	23	0.9	3.40E-05	3.70E-03
GOTERM_BP_FAT	activation of plasma proteins involved in acute inflammatory response	RT	16	0.6	3.80E-05	4.10E-03
GOTERM_BP_FAT	complement activation	RT	16	0.6	3.80E-05	4.10E-03
GOTERM_BP_FAT	hexose biosynthetic process	RT	13	0.5	4.20E-05	4.40E-03
GOTERM_BP_FAT	inflammatory response	RT	54	2	5.20E-05	5.20E-03
GOTERM_BP_FAT	organic acid catabolic process	RT	26	1	5.90E-05	5.80E-03
GOTERM_BP_FAT	carboxylic acid catabolic process	RT	26	1	5.90E-05	5.80E-03

GOTERM_BP_FAT	activation of immune response	RT	27	1	6.20E-05	6.00E-03
GOTERM_BP_FAT	cellular amino acid derivative metabolic process	RT	38	1.4	6.50E-05	6.10E-03
GOTERM_BP_FAT	protein maturation	RT	29	1.1	6.80E-05	6.20E-03
GOTERM_BP_FAT	complement activation, classical pathway	RT	14	0.5	7.70E-05	6.90E-03
GOTERM_BP_FAT	nitrogen compound catabolic process	RT	17	0.6	7.90E-05	6.90E-03
GOTERM_BP_FAT	amine biosynthetic process	RT	24	0.9	8.10E-05	6.90E-03
GOTERM_BP_FAT	nitrogen compound biosynthetic process	RT	67	2.5	8.10E-05	6.80E-03
GOTERM_BP_FAT	intracellular transport	RT	89	3.4	8.30E-05	6.80E-03
GOTERM_BP_FAT	cholesterol biosynthetic process	RT	12	0.5	9.30E-05	7.50E-03
GOTERM_BP_FAT	amine catabolic process	RT	22	0.8	1.10E-04	8.50E-03
GOTERM_BP_FAT	monosaccharide biosynthetic process	RT	14	0.5	1.20E-04	9.00E-03
GOTERM_BP_FAT	humoral immune response mediated by circulating immunoglobulin	RT	15	0.6	1.20E-04	8.90E-03
GOTERM_BP_FAT	glucose metabolic process	RT	37	1.4	1.30E-04	9.30E-03
GOTERM_BP_FAT	protein processing	RT	27	1	1.40E-04	1.00E-02
GOTERM_BP_FAT	immune effector process	RT	34	1.3	1.60E-04	1.20E-02
GOTERM_BP_FAT	cellular response to nutrient levels	RT	13	0.5	1.70E-04	1.20E-02
GOTERM_BP_FAT	pyridine nucleotide metabolic process	RT	13	0.5	1.70E-04	1.20E-02
GOTERM_BP_FAT	nucleobase, nucleoside and nucleotide catabolic process	RT	15	0.6	1.70E-04	1.20E-02
GOTERM_BP_FAT	nucleobase, nucleoside, nucleotide and nucleic acid catabolic process	RT	15	0.6	1.70E-04	1.20E-02
GOTERM_BP_FAT	positive regulation of response to stimulus	RT	45	1.7	1.90E-04	1.30E-02
GOTERM_BP_FAT	cellular response to extracellular stimulus	RT	17	0.6	2.00E-04	1.30E-02
GOTERM_BP_FAT	humoral immune response	RT	19	0.7	2.10E-04	1.40E-02
GOTERM_BP_FAT	response to extracellular stimulus	RT	35	1.3	2.20E-04	1.40E-02
GOTERM_BP_FAT	pyruvate metabolic process	RT	12	0.5	2.30E-04	1.50E-02
GOTERM_BP_FAT	glycerolipid metabolic process	RT	34	1.3	2.60E-04	1.60E-02
GOTERM_BP_FAT	cellular carbohydrate biosynthetic process	RT	19	0.7	3.50E-04	2.20E-02
GOTERM_BP_FAT	fat cell differentiation	RT	20	0.8	3.90E-04	2.30E-02
GOTERM_BP_FAT	cellular hormone metabolic process	RT	18	0.7	4.10E-04	2.40E-02
GOTERM_BP_FAT	establishment of protein localization	RT	122	4.6	4.20E-04	2.50E-02
GOTERM_BP_FAT	blood vessel development	RT	54	2	4.60E-04	2.60E-02
GOTERM_BP_FAT	protein transport	RT	121	4.6	4.60E-04	2.60E-02
GOTERM_BP_FAT	antigen processing and presentation of peptide antigen	RT	14	0.5	4.90E-04	2.70E-02
GOTERM_BP_FAT	innate immune response	RT	29	1.1	5.00E-04	2.70E-02
GOTERM_BP_FAT	glycerol metabolic process	RT	11	0.4	5.10E-04	2.70E-02
GOTERM_BP_FAT	antigen processing and presentation of exogenous peptide antigen	RT	11	0.4	5.10E-04	2.70E-02
GOTERM_BP_FAT	nucleotide catabolic process	RT	13	0.5	5.20E-04	2.70E-02
GOTERM_BP_FAT	regulation of programmed cell death	RT	106	4	5.60E-04	2.90E-02
GOTERM_BP_FAT	protein localization	RT	136	5.2	6.60E-04	3.40E-02
GOTERM_BP_FAT	regulation of cell death	RT	106	4	6.70E-04	3.40E-02
GOTERM_BP_FAT	cellular amino acid catabolic process	RT	18	0.7	6.70E-04	3.40E-02
GOTERM_BP_FAT	gluconeogenesis	RT	10	0.4	7.20E-04	3.50E-02
GOTERM_BP_FAT	oligosaccharide metabolic process	RT	10	0.4	7.20E-04	3.50E-02
GOTERM_BP_FAT	regulation of coagulation	RT	10	0.4	7.20E-04	3.50E-02
GOTERM_BP_FAT	response to hypoxia	RT	20	0.8	7.50E-04	3.70E-02
GOTERM_BP_FAT	regulation of apoptosis	RT	104	3.9	7.60E-04	3.70E-02
GOTERM_BP_FAT	response to nutrient levels	RT	30	1.1	7.70E-04	3.70E-02
GOTERM_BP_FAT	fat-soluble vitamin biosynthetic process	RT	6	0.2	8.30E-04	3.90E-02
GOTERM_BP_FAT	vasculature development	RT	54	2	8.30E-04	3.80E-02
GOTERM_BP_FAT	negative regulation of lipid metabolic process	RT	7	0.3	8.80E-04	4.00E-02
GOTERM_BP_FAT	alcohol biosynthetic process	RT	14	0.5	9.00E-04	4.10E-02
GOTERM_BP_FAT	response to oxygen levels	RT	20	0.8	9.30E-04	4.10E-02
GOTERM_BP_FAT	angiogenesis	RT	33	1.2	1.00E-03	4.50E-02
GOTERM_BP_FAT	brown fat cell differentiation	RT	12	0.5	1.10E-03	4.70E-02
GOTERM_BP_FAT	alditol metabolic process	RT	11	0.4	1.10E-03	4.80E-02
GOTERM_BP_FAT	oxidoreduction coenzyme metabolic process	RT	14	0.5	1.20E-03	5.10E-02
GOTERM_BP_FAT	defense response	RT	86	3.3	1.20E-03	5.20E-02
GOTERM_BP_FAT	response to oxidative stress	RT	24	0.9	1.30E-03	5.50E-02
GOTERM_BP_FAT	acylglycerol metabolic process	RT	15	0.6	1.40E-03	5.60E-02
GOTERM_BP_FAT	organic ether metabolic process	RT	16	0.6	1.50E-03	6.00E-02
GOTERM_BP_FAT	cellular amide metabolic process	RT	14	0.5	1.60E-03	6.30E-02
GOTERM_BP_FAT	ribonucleoside metabolic process	RT	14	0.5	1.60E-03	6.30E-02
GOTERM_BP_FAT	isoprenoid biosynthetic process	RT	10	0.4	1.60E-03	6.50E-02
GOTERM_BP_FAT	response to hormone stimulus	RT	38	1.4	1.70E-03	6.70E-02
GOTERM_BP_FAT	regulation of cell-substrate adhesion	RT	14	0.5	2.00E-03	7.80E-02
GOTERM_BP_FAT	lipid localization	RT	31	1.2	2.20E-03	8.40E-02
GOTERM_BP_FAT	aromatic compound catabolic process	RT	8	0.3	2.20E-03	8.30E-02
GOTERM_BP_FAT	glutamine family amino acid biosynthetic process	RT	8	0.3	2.20E-03	8.30E-02
GOTERM_BP_FAT	neutral lipid metabolic process	RT	15	0.6	2.20E-03	8.20E-02
GOTERM_BP_FAT	glycerol ether metabolic process	RT	15	0.6	2.20E-03	8.20E-02
GOTERM_BP_FAT	generation of precursor metabolites and energy	RT	54	2	2.30E-03	8.30E-02
GOTERM_BP_FAT	regulation of cell cycle	RT	46	1.7	2.30E-03	8.50E-02
GOTERM_BP_FAT	lipid catabolic process	RT	32	1.2	2.30E-03	8.40E-02
GOTERM_BP_FAT	triglyceride metabolic process	RT	13	0.5	2.40E-03	8.40E-02
GOTERM_BP_FAT	alcohol catabolic process	RT	19	0.7	2.40E-03	8.60E-02
GOTERM_BP_FAT	cellular carbohydrate catabolic process	RT	18	0.7	2.40E-03	8.60E-02

GOTERM_BP_FAT	cellular protein localization	RT	60	2.3	2.70E-03	9.20E-02
GOTERM_BP_FAT	cofactor catabolic process	RT	12	0.5	2.70E-03	9.20E-02
GOTERM_BP_FAT	lipid transport	RT	29	1.1	2.90E-03	9.70E-02
GOTERM_BP_FAT	cellular macromolecule localization	RT	60	2.3	3.10E-03	1.00E-01
GOTERM_BP_FAT	glutathione metabolic process	RT	10	0.4	3.30E-03	1.10E-01
GOTERM_BP_FAT	alkaloid metabolic process	RT	10	0.4	3.30E-03	1.10E-01
GOTERM_BP_FAT	nicotinamide metabolic process	RT	10	0.4	3.30E-03	1.10E-01
GOTERM_BP_FAT	purine nucleoside metabolic process	RT	10	0.4	3.30E-03	1.10E-01
GOTERM_BP_FAT	purine ribonucleoside metabolic process	RT	10	0.4	3.30E-03	1.10E-01
GOTERM_BP_FAT	nicotinamide nucleotide metabolic process	RT	10	0.4	3.30E-03	1.10E-01
GOTERM_BP_FAT	antigen processing and presentation of exogenous peptide antigen via MHC class II	RT	8	0.3	3.50E-03	1.10E-01
GOTERM_BP_FAT	antigen processing and presentation of peptide antigen via MHC class II	RT	8	0.3	3.50E-03	1.10E-01
GOTERM_BP_FAT	apoptosis	RT	86	3.3	3.70E-03	1.20E-01
GOTERM_BP_FAT	carbohydrate biosynthetic process	RT	22	0.8	3.70E-03	1.20E-01
GOTERM_BP_FAT	negative regulation of coagulation	RT	6	0.2	3.90E-03	1.20E-01
GOTERM_BP_FAT	peptide metabolic process	RT	13	0.5	3.90E-03	1.20E-01
GOTERM_BP_FAT	coenzyme catabolic process	RT	11	0.4	4.10E-03	1.30E-01
GOTERM_BP_FAT	response to starvation	RT	11	0.4	4.10E-03	1.30E-01
GOTERM_BP_FAT	glutamine family amino acid metabolic process	RT	14	0.5	4.20E-03	1.30E-01
GOTERM_BP_FAT	polyol metabolic process	RT	14	0.5	4.20E-03	1.30E-01
GOTERM_BP_FAT	9-cis-retinoic acid biosynthetic process	RT	5	0.2	4.30E-03	1.30E-01
GOTERM_BP_FAT	9-cis-retinoic acid metabolic process	RT	5	0.2	4.30E-03	1.30E-01
GOTERM_BP_FAT	vitamin A biosynthetic process	RT	5	0.2	4.30E-03	1.30E-01
GOTERM_BP_FAT	proteolysis	RT	173	6.6	4.40E-03	1.30E-01
GOTERM_BP_FAT	cell death	RT	92	3.5	4.70E-03	1.40E-01
GOTERM_BP_FAT	intracellular protein transport	RT	55	2.1	4.70E-03	1.40E-01
GOTERM_BP_FAT	blood vessel morphogenesis	RT	42	1.6	4.70E-03	1.40E-01
GOTERM_BP_FAT	hormone metabolic process	RT	23	0.9	4.80E-03	1.40E-01
GOTERM_BP_FAT	wound healing	RT	27	1	4.80E-03	1.40E-01
GOTERM_BP_FAT	ribosome biogenesis	RT	27	1	4.80E-03	1.40E-01
GOTERM_BP_FAT	coenzyme biosynthetic process	RT	18	0.7	5.10E-03	1.40E-01
GOTERM_BP_FAT	cellular aldehyde metabolic process	RT	8	0.3	5.20E-03	1.50E-01
GOTERM_BP_FAT	response to molecule of bacterial origin	RT	15	0.6	5.30E-03	1.50E-01
GOTERM_BP_FAT	organophosphate metabolic process	RT	38	1.4	5.40E-03	1.50E-01
GOTERM_BP_FAT	cofactor biosynthetic process	RT	23	0.9	5.50E-03	1.50E-01
GOTERM_BP_FAT	regulation of T cell activation	RT	26	1	5.80E-03	1.60E-01
GOTERM_BP_FAT	programmed cell death	RT	86	3.3	5.90E-03	1.60E-01
GOTERM_BP_FAT	carbohydrate catabolic process	RT	21	0.8	6.10E-03	1.60E-01
GOTERM_BP_FAT	death	RT	93	3.5	6.40E-03	1.70E-01
GOTERM_BP_FAT	positive regulation of programmed cell death	RT	50	1.9	6.60E-03	1.70E-01
GOTERM_BP_FAT	response to endogenous stimulus	RT	39	1.5	6.60E-03	1.70E-01
GOTERM_BP_FAT	negative regulation of programmed cell death	RT	49	1.9	6.60E-03	1.70E-01
GOTERM_BP_FAT	antigen processing and presentation	RT	22	0.8	6.70E-03	1.70E-01
GOTERM_BP_FAT	response to protein stimulus	RT	22	0.8	6.70E-03	1.70E-01
GOTERM_BP_FAT	serine family amino acid metabolic process	RT	9	0.3	6.90E-03	1.80E-01
GOTERM_BP_FAT	water-soluble vitamin biosynthetic process	RT	9	0.3	6.90E-03	1.80E-01
GOTERM_BP_FAT	autophagy	RT	11	0.4	6.90E-03	1.80E-01
GOTERM_BP_FAT	negative regulation of cell death	RT	49	1.9	7.20E-03	1.80E-01
GOTERM_BP_FAT	negative regulation of apoptosis	RT	48	1.8	7.20E-03	1.80E-01
GOTERM_BP_FAT	ethanolamine and derivative metabolic process	RT	8	0.3	7.50E-03	1.80E-01
GOTERM_BP_FAT	immune response	RT	85	3.2	7.60E-03	1.80E-01
GOTERM_BP_FAT	actin filament organization	RT	16	0.6	7.60E-03	1.80E-01
GOTERM_BP_FAT	nucleoside metabolic process	RT	16	0.6	7.60E-03	1.80E-01
GOTERM_BP_FAT	protein targeting	RT	30	1.1	7.70E-03	1.80E-01
GOTERM_BP_FAT	'de novo' posttranslational protein folding	RT	7	0.3	7.70E-03	1.80E-01
GOTERM_BP_FAT	'de novo' protein folding	RT	7	0.3	7.70E-03	1.80E-01
GOTERM_BP_FAT	regulation of blood coagulation	RT	7	0.3	7.70E-03	1.80E-01
GOTERM_BP_FAT	NADP metabolic process	RT	7	0.3	7.70E-03	1.80E-01
GOTERM_BP_FAT	positive regulation of cell death	RT	50	1.9	7.70E-03	1.80E-01
GOTERM_BP_FAT	sulfur metabolic process	RT	23	0.9	8.20E-03	1.90E-01
GOTERM_BP_FAT	negative regulation of multicellular organismal process	RT	24	0.9	8.60E-03	2.00E-01
GOTERM_BP_FAT	positive regulation of T cell differentiation	RT	11	0.4	8.90E-03	2.00E-01
GOTERM_BP_FAT	antigen processing and presentation via MHC class Ib	RT	5	0.2	9.00E-03	2.10E-01
GOTERM_BP_FAT	glucose catabolic process	RT	15	0.6	9.30E-03	2.10E-01
GOTERM_BP_FAT	hexose catabolic process	RT	15	0.6	9.30E-03	2.10E-01
GOTERM_BP_FAT	vacuolar transport	RT	9	0.3	9.30E-03	2.10E-01
GOTERM_BP_FAT	cellular response to starvation	RT	9	0.3	9.30E-03	2.10E-01
GOTERM_BP_FAT	negative regulation of steroid metabolic process	RT	4	0.2	9.50E-03	2.10E-01
GOTERM_BP_FAT	cellular response to nutrient	RT	4	0.2	9.50E-03	2.10E-01
GOTERM_BP_FAT	negative regulation of steroid biosynthetic process	RT	4	0.2	9.50E-03	2.10E-01
GOTERM_BP_FAT	negative regulation of catalytic activity	RT	24	0.9	9.80E-03	2.20E-01
GOTERM_BP_FAT	DNA packaging	RT	24	0.9	9.80E-03	2.20E-01

Supporting Table S4. DAVID Analysis of Gene Ontology (Cellular Components)

Category	Term	RT	Count	%	P-Value	Benjamini
GOTERM_CC_FAT	endoplasmic reticulum	RT	227	8.6	1.10E-24	6.30E-22
GOTERM_CC_FAT	mitochondrion	RT	302	11.4	4.80E-20	1.40E-17
GOTERM_CC_FAT	organelle membrane	RT	206	7.8	5.30E-19	1.00E-16
GOTERM_CC_FAT	cell fraction	RT	150	5.7	2.70E-13	3.80E-11
GOTERM_CC_FAT	microsome	RT	63	2.4	1.10E-12	1.20E-10
GOTERM_CC_FAT	vesicular fraction	RT	64	2.4	1.70E-12	1.60E-10
GOTERM_CC_FAT	mitochondrial part	RT	129	4.9	7.60E-11	6.20E-09
GOTERM_CC_FAT	organelle inner membrane	RT	87	3.3	2.10E-10	1.50E-08
GOTERM_CC_FAT	endoplasmic reticulum part	RT	70	2.7	3.20E-10	2.00E-08
GOTERM_CC_FAT	envelope	RT	130	4.9	4.00E-10	2.30E-08
GOTERM_CC_FAT	organelle envelope	RT	129	4.9	6.10E-10	3.20E-08
GOTERM_CC_FAT	mitochondrial envelope	RT	100	3.8	1.50E-09	7.30E-08
GOTERM_CC_FAT	soluble fraction	RT	39	1.5	1.60E-09	7.00E-08
GOTERM_CC_FAT	mitochondrial inner membrane	RT	81	3.1	2.50E-09	1.00E-07
GOTERM_CC_FAT	mitochondrial membrane	RT	94	3.6	5.40E-09	2.00E-07
GOTERM_CC_FAT	insoluble fraction	RT	121	4.6	2.90E-08	1.00E-06
GOTERM_CC_FAT	peroxisome	RT	37	1.4	9.90E-08	3.30E-06
GOTERM_CC_FAT	microbody	RT	37	1.4	9.90E-08	3.30E-06
GOTERM_CC_FAT	cytosol	RT	122	4.6	1.50E-07	4.90E-06
GOTERM_CC_FAT	membrane fraction	RT	115	4.4	1.70E-07	5.00E-06
GOTERM_CC_FAT	endomembrane system	RT	116	4.4	1.20E-06	3.40E-05
GOTERM_CC_FAT	lysosome	RT	50	1.9	1.70E-06	4.60E-05
GOTERM_CC_FAT	lytic vacuole	RT	50	1.9	2.00E-06	5.30E-05
GOTERM_CC_FAT	vacuole	RT	54	2	4.40E-06	1.10E-04
GOTERM_CC_FAT	endoplasmic reticulum membrane	RT	43	1.6	8.30E-06	2.00E-04
GOTERM_CC_FAT	membrane-enclosed lumen	RT	217	8.2	8.60E-06	2.00E-04
GOTERM_CC_FAT	organelle lumen	RT	209	7.9	1.80E-05	3.90E-04
GOTERM_CC_FAT	intracellular organelle lumen	RT	208	7.9	2.20E-05	4.50E-04
GOTERM_CC_FAT	mitochondrial matrix	RT	44	1.7	2.30E-05	4.60E-04
GOTERM_CC_FAT	mitochondrial lumen	RT	44	1.7	2.30E-05	4.60E-04
GOTERM_CC_FAT	nuclear envelope-endoplasmic reticulum network	RT	43	1.6	3.20E-05	6.30E-04
GOTERM_CC_FAT	pigment granule	RT	26	1	1.90E-04	3.50E-03
GOTERM_CC_FAT	melanosome	RT	26	1	1.90E-04	3.50E-03
GOTERM_CC_FAT	endoplasmic reticulum lumen	RT	23	0.9	2.40E-04	4.50E-03
GOTERM_CC_FAT	endosome	RT	57	2.2	2.70E-04	4.80E-03
GOTERM_CC_FAT	lipid particle	RT	8	0.3	8.50E-04	1.50E-02
GOTERM_CC_FAT	integral to organelle membrane	RT	25	0.9	9.90E-04	1.70E-02
GOTERM_CC_FAT	integral to endoplasmic reticulum membrane	RT	13	0.5	1.20E-03	1.90E-02
GOTERM_CC_FAT	actin cytoskeleton	RT	46	1.7	1.30E-03	2.10E-02
GOTERM_CC_FAT	myosin complex	RT	19	0.7	1.40E-03	2.10E-02
GOTERM_CC_FAT	intrinsic to organelle membrane	RT	29	1.1	1.40E-03	2.10E-02
GOTERM_CC_FAT	intrinsic to endoplasmic reticulum membrane	RT	17	0.6	1.50E-03	2.20E-02
GOTERM_CC_FAT	microbody membrane	RT	11	0.4	1.80E-03	2.60E-02
GOTERM_CC_FAT	peroxisomal membrane	RT	11	0.4	1.80E-03	2.60E-02
GOTERM_CC_FAT	peroxisomal part	RT	12	0.5	2.30E-03	3.20E-02
GOTERM_CC_FAT	microbody part	RT	12	0.5	2.30E-03	3.20E-02
GOTERM_CC_FAT	Golgi apparatus	RT	123	4.7	2.40E-03	3.30E-02
GOTERM_CC_FAT	plasma lipoprotein particle	RT	11	0.4	2.50E-03	3.30E-02
GOTERM_CC_FAT	protein-lipid complex	RT	11	0.4	2.50E-03	3.30E-02
GOTERM_CC_FAT	sarcolemma	RT	15	0.6	4.10E-03	5.20E-02
GOTERM_CC_FAT	extrinsic to membrane	RT	88	3.3	4.20E-03	5.20E-02
GOTERM_CC_FAT	nuclear membrane	RT	13	0.5	4.50E-03	5.50E-02
GOTERM_CC_FAT	monolayer-surrounded lipid storage body	RT	5	0.2	4.60E-03	5.50E-02
GOTERM_CC_FAT	ribonucleoprotein complex	RT	86	3.3	5.00E-03	5.70E-02
GOTERM_CC_FAT	contractile fiber	RT	24	0.9	5.60E-03	6.30E-02
GOTERM_CC_FAT	late endosome	RT	14	0.5	6.00E-03	6.60E-02
GOTERM_CC_FAT	nuclear periphery	RT	15	0.6	6.20E-03	6.70E-02
GOTERM_CC_FAT	sarcomere	RT	21	0.8	6.40E-03	6.80E-02
GOTERM_CC_FAT	contractile fiber part	RT	22	0.8	7.10E-03	7.40E-02
GOTERM_CC_FAT	vesicle	RT	94	3.6	7.30E-03	7.40E-02
GOTERM_CC_FAT	membrane-bounded vesicle	RT	78	3	7.80E-03	7.80E-02
GOTERM_CC_FAT	extracellular space	RT	92	3.5	9.20E-03	9.00E-02

Supporting Table S5. DAVID Analysis of KEGG Pathways

Category	Term	RT	Count	%	P-Value	Benjamini
KEGG_PATHWAY	Drug metabolism	RT	42	1.6	1.40E-13	2.70E-11
KEGG_PATHWAY	Metabolism of xenobiotics by cytochrome P450	RT	36	1.4	2.90E-11	2.70E-09

KEGG_PATHWAY	Retinol metabolism	RT	34	1.3	2.20E-09	1.40E-07
KEGG_PATHWAY	Glutathione metabolism	RT	24	0.9	4.60E-06	2.20E-04
KEGG_PATHWAY	Glycine, serine and threonine metabolism	RT	17	0.6	2.00E-05	7.60E-04
KEGG_PATHWAY	Complement and coagulation cascades	RT	29	1.1	2.30E-05	7.20E-04
KEGG_PATHWAY	PPAR signaling pathway	RT	28	1.1	1.90E-04	5.00E-03
KEGG_PATHWAY	Fatty acid metabolism	RT	19	0.7	2.40E-04	5.70E-03
KEGG_PATHWAY	Steroid hormone biosynthesis	RT	17	0.6	2.30E-03	4.80E-02
KEGG_PATHWAY	Glyoxylate and dicarboxylate metabolism	RT	9	0.3	2.60E-03	4.80E-02
KEGG_PATHWAY	Synthesis and degradation of ketone bodies	RT	7	0.3	2.90E-03	4.80E-02
KEGG_PATHWAY	Valine, leucine and isoleucine degradation	RT	17	0.6	3.00E-03	4.70E-02
KEGG_PATHWAY	Prostate cancer	RT	27	1	3.90E-03	5.60E-02
KEGG_PATHWAY	Steroid biosynthesis	RT	9	0.3	4.20E-03	5.50E-02
KEGG_PATHWAY	Amino sugar and nucleotide sugar metabolism	RT	16	0.6	5.00E-03	6.20E-02
KEGG_PATHWAY	Lysosome	RT	33	1.2	5.00E-03	5.80E-02
KEGG_PATHWAY	Arginine and proline metabolism	RT	18	0.7	5.90E-03	6.40E-02
KEGG_PATHWAY	Hypertrophic cardiomyopathy (HCM)	RT	25	0.9	6.40E-03	6.50E-02
KEGG_PATHWAY	Systemic lupus erythematosus	RT	29	1.1	7.20E-03	6.90E-02
KEGG_PATHWAY	Primary bile acid biosynthesis	RT	8	0.3	7.90E-03	7.20E-02