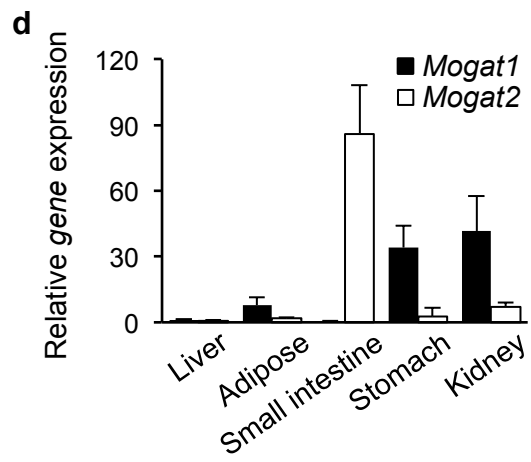


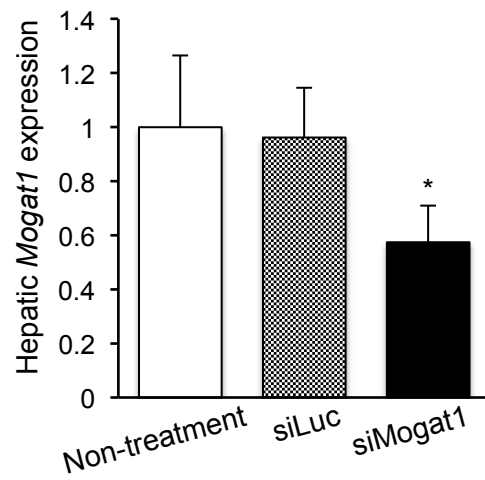
**Figure S1. Microarray data analyses for the extraction of potential candidate genes.**

(a) Scatter plot of differentially expressed genes between type2 diabetic and normal mice. Among the 41174 entities present on the Whole Mouse Genome microarray (Agilent), 1285 (526 and 759 were up- or down-regulated, respectively) were considered to be diabetes-dependent and age-dependent entities in diabetic mice, while 895 (163 and 732 were up- or down-regulated, respectively) were considered to be age-dependent in normal mice. (b) Of the 759 entities that were down-regulated in 11w compared to 4w KKAy mice, 453 and 306 were determined to be diabetes-dependent, and age-dependent entities, respectively. (c) Ven diagram for selection of entities annotated with the GO term lipid metabolic process. 46 and 62 were determined to be diabetes-dependent up- and down-regulated entities those were annotated with lipid metabolic process.



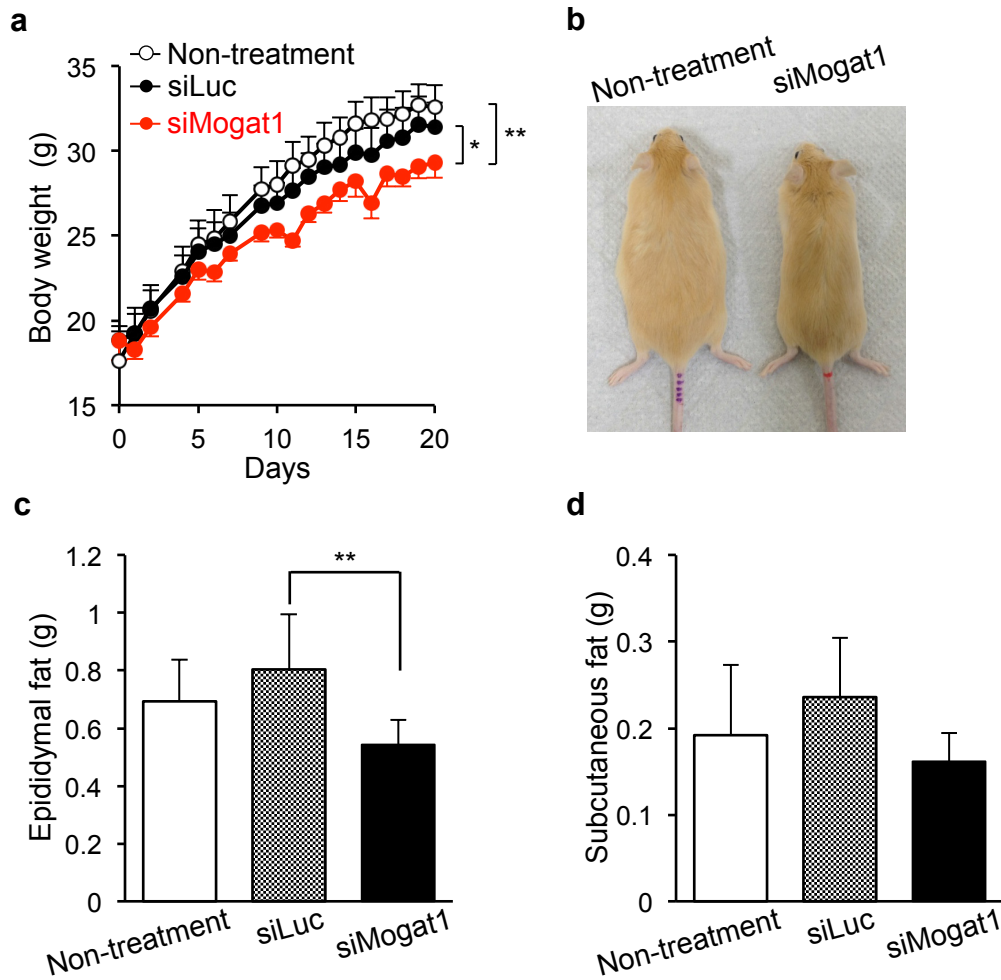
**Figure S2. Expression of *Mogat1* or *Mogat2* mRNA in several tissues of pre-diabetic KKAY mice.**

The expression of *Mogat1* mRNA in liver was analyzed by quantitative RT-PCR. Means  $\pm$  SD are shown (n=5).



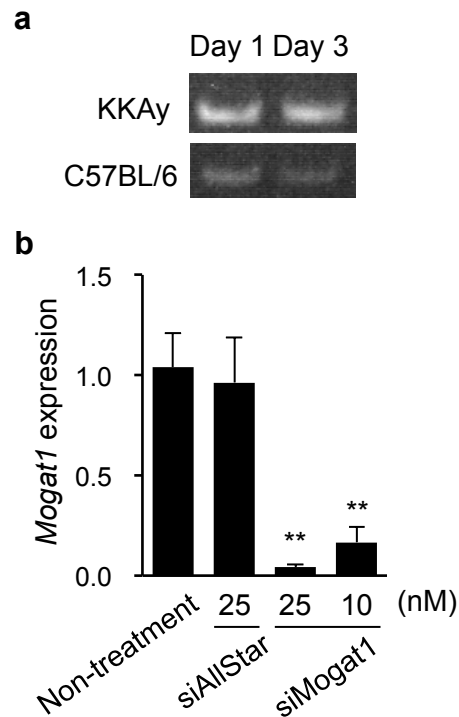
**Figure S3. *in vivo* silencing of hepatic *Mogat1* expression via a systemic siRNA delivery system.**

*Mogat1* mRNA levels in the liver at 12 days after the intravenous injection of nanoparticles loaded with siMogat1 or siLuc (n=5) were analyzed by a quantitative RT-PCR. The expression levels in non-treated mice (n=5) were also assessed. Data represent mean ± SD. \*P<0.05, vs non-treatment control (One-way ANOVA followed by Dunnett's test).



**Figure S4. Changes in body weight after siMogat1 treatment.**

(a) Monitoring of body weight. 4-5 week old KKAY mice were treated with siMogat1 or siLuc loaded nanoparticles every 5 days (2 mg/kg each). (b) Representative image picture of KKAY mouse at Day 20. (c) Epididymal and (d) subcutaneous fat amount at Day 20. Means  $\pm$  SD are shown (n=5-6). \*P<0.05, \*\*P<0.01 (One-way ANOVA followed by Tukey-Kramer's HSD test).



**Figure S5. siRNA transfection study of mouse primary hepatocytes.**

(a) *Mogat1* expression in primary hepatocytes of 9-week old KKAY and C57BL/6J mouse. *Mogat1* expression was evaluated at Day 1 and Day 3 after cell seeding. The PCR products of *Mogat1* were subjected to 10% native gel electrophoresis and visualized by EtBr staining. (b) Knockdown effect of siMogat1 in primary hepatocytes. Isolated hepatocytes from 9-week old KKAY were transfected with the indicated concentrations of siRNA by using a commercially available HiPerFect transfection reagent (QIAGEN). *Mogat1* mRNA levels normalized to *Actb* mRNA measured 48 hours after siRNA transfection (n = 3). Means  $\pm$  SD are shown for all panels. \*\*P<0.01 vs. non-treatment (One-way ANOVA followed by a Dunnett's test).

**Table S1. Gene Ontology analysis of 413 entities that were up-regulated in diabetic mice**

GO category	GO terms
Biological Process	lipid biosynthetic process lipid metabolic process sterol metabolic process negative regulation of lipid metabolic process response to protein stimulus chromatin assembly nucleosome organization cellular lipid metabolic process response to unfolded protein regulation of developmental process
Cellular Component	endoplasmic reticulum nucleosome extracellular region protein-DNA complex chromatin endoplasmic reticulum part mitochondrion insoluble fraction cell fraction axon part
Molecular Function	oxidoreductase activity, acting on the CH-OH group of donors, NAD or NADP as acceptor steroid dehydrogenase activity, acting on the CH-OH group of donors, NAD or NADP as acceptor hydro-lyase activity carboxy-lyase activity pyridoxal phosphate binding vitamin B6 binding FAD binding NAD or NADH binding transferase activity, transferring acyl groups other than amino-acyl groups secondary active transmembrane transporter activity

Gene Ontology (GO) analysis of the diabetes-dependent up-regulated 413 entities was carried out using the Database for Annotation, Visualization and Integrated Discovery (DAVID, <http://david.abcc.ncifcrf.gov>). The top 10 functionally enriched GO terms ranked by p-value for GOTERM\_BP\_3, GOTERM\_CC\_3 and GOTERM\_MF\_3 were shown.

**Table S2. Gene Ontology analysis of 453 entities that were down-regulated in diabetic mice**

GO category	GO terms
Biological Process	lipid metabolic process
	oxoacid metabolic process
	organic acid metabolic process
	cellular ketone metabolic process
	regulation of catalytic activity
	regulation of transferase activity
	positive regulation of catalytic activity
	positive regulation of molecular function
	steroid metabolic process
	cellular lipid metabolic process
Cellular Component	vesicular fraction
	microsome
	cell fraction
	insoluble fraction
	membrane fraction
	plasma membrane
	extracellular region
	cytosol
	extracellular region part
	extrinsic to membrane
Molecular Function	phosphoric diester hydrolase activity
	aryl sulfotransferase activity
	iron ion binding
	kinase regulator activity
	carboxylesterase activity
	growth factor activity
	heme binding
	lipase activity
	tetrapyrrole binding
	protein kinase regulator activity

Gene Ontology (GO) analysis of the diabetes-dependent down-regulated 453 entities was carried out using DAVID. The top 10 functionally enriched GO terms ranked by p-value for GOTERM\_BP\_3, GOTERM\_CC\_3 and GOTERM\_MF\_3 were shown.

**Table S3. 46 entities with lipid metabolic process out of the diabetes-dependent up-regulated entities**

Probe Name	Gene Symbol	Description	Fold Change		
			11w KKAy / 11w C57	11w KKAy / 4w KKAy	11w C57 / 4w C57
A_52_P364021	<i>Mogat1</i>	monoacylglycerol O-acyltransferase 1	19.4	4.3	1.6
A_51_P352005	<i>Hsd3b4</i>	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 4	17.7	36.7	1.3
A_51_P496162	<i>Hsd3b5</i>	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 5	16.5	37.5	1.3
A_51_P199168	<i>Cidea</i>	cell death-inducing DNA fragmentation factor, alpha subunit-like effector A	15.2	10.9	1.1
A_51_P112151	<i>Mogat1</i>	monoacylglycerol O-acyltransferase 1	14.9	4.3	1.3
A_52_P64376	<i>Mogat1</i>	monoacylglycerol O-acyltransferase 1	12.2	4.4	1.3
A_51_P457664	<i>Cyp46a1</i>	cytochrome P450, family 46, subfamily a, polypeptide 1	9.8	3.5	1.5
A_51_P475523	<i>Brcal</i>	breast cancer 1	6.1	2.8	0.7
A_51_P375138	<i>Cd36</i>	CD36 antigen	3.4	2.8	0.8
A_51_P226567	<i>Hsd3b2</i>	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 2	3.4	2.0	0.7
A_51_P375146	<i>Cd36</i>	CD36 antigen	3.3	3.0	0.9
A_52_P67637	<i>Sc5d</i>	sterol-C5-desaturase (fungal ERG3, delta-5-desaturase) homolog (S. cerevisiae)	3.3	2.1	1.7
A_51_P470935	<i>Bdh2</i>	3-hydroxybutyrate dehydrogenase, type 2	3.0	3.7	1.2
A_52_P407786	<i>Sptlc2</i>	serine palmitoyltransferase, long chain base subunit 2	2.9	3.3	1.3
A_52_P682382	<i>Scd1</i>	stearoyl-Coenzyme A desaturase 1	2.8	5.1	1.0
A_52_P195809	<i>Bdh2</i>	3-hydroxybutyrate dehydrogenase, type 2	2.8	3.8	1.2
A_51_P382764	<i>Akr1c20</i>	aldo-keto reductase family 1, member C20	2.8	2.5	0.8
A_51_P290207	<i>Insig1</i>	insulin induced gene 1	2.7	2.4	1.3
A_51_P189082	<i>Akr1c6</i>	aldo-keto reductase family 1, member C6	2.7	2.3	0.8
A_51_P189442	<i>Adh4</i>	alcohol dehydrogenase 4 (class II), pi polypeptide	2.6	3.9	1.1
A_51_P318262	<i>Hao1</i>	hydroxyacid oxidase 1, liver	2.6	2.3	0.7
A_51_P355943	<i>Mvd</i>	mevalonate (diphospho) decarboxylase	2.6	2.1	1.3



**Table S3. Continued**

Probe Name	Gene Symbol	Description	Fold Change		
			11w KKAy / 11w C57	11w KKAy / 4w KKAy	11w C57 / 4w C57
A_51_P499854	<i>Ghr</i>	growth hormone receptor	2.4	2.4	1.1
A_52_P644613	<i>Sult1b1</i>	sulfotransferase family 1B, member 1	2.3	2.9	1.0
A_51_P206551	<i>Sult1b1</i>	sulfotransferase family 1B, member 1	2.2	2.3	0.9
A_51_P340226	<i>Sh3yl1</i>	Sh3 domain YSC-like 1	2.2	2.2	1.1
A_51_P458839	<i>Piga</i>	phosphatidylinositol glycan anchor biosynthesis, class A	2.1	2.1	1.1
A_52_P562676	<i>Sult4a1</i>	sulfotransferase family 4A, member 1	1.9	2.1	1.2
A_52_P680941	<i>Ghr</i>	growth hormone receptor	1.9	2.3	1.0
A_52_P391095	<i>Crem</i>	cAMP responsive element modulator	1.9	2.6	1.1
A_51_P379798	<i>Fdps</i>	farnesyl diphosphate synthetase	1.8	2.7	1.1
A_52_P391098	<i>Crem</i>	cAMP responsive element modulator	1.8	2.5	1.1
A_51_P267024	<i>Pafah1b3</i>	platelet-activating factor acetylhydrolase, isoform 1b, subunit 3	1.8	2.0	1.0
A_52_P391103	<i>Crem</i>	cAMP responsive element modulator	1.8	2.6	1.1
A_52_P680935	<i>Ghr</i>	growth hormone receptor	1.8	2.3	1.1
A_51_P240857	<i>Chpt1</i>	choline phosphotransferase 1	1.7	2.5	1.8
A_52_P460957	<i>Crem</i>	cAMP responsive element modulator	1.7	2.4	1.0
A_51_P423976	<i>Crem</i>	cAMP responsive element modulator	1.7	3.3	1.3
A_52_P655803	<i>Chpt1</i>	choline phosphotransferase 1	1.6	2.2	1.7
A_52_P164161	<i>Cyp51</i>	cytochrome P450, family 51	1.6	3.1	1.4
A_51_P329711	<i>Idi1</i>	isopentenyl-diphosphate delta isomerase	1.5	3.0	1.3
A_52_P441634	<i>Idi1</i>	isopentenyl-diphosphate delta isomerase	1.4	2.1	1.1
A_52_P231292	<i>Cyp2j6</i>	cytochrome P450, family 2, subfamily j, polypeptide 6	1.4	2.1	1.3
A_51_P187346	<i>Sgms2</i>	sphingomyelin synthase 2	1.4	2.2	1.4

**Table S3. Continued**

Probe Name	Gene Symbol	Description	Fold Change		
			11w KKAy / 11w C57	11w KKAy / 4w KKAy	11w C57 / 4w C57
A_51_P209372	<i>Sc4mol</i>	sterol-C4-methyl oxidase-like	1.1	2.4	1.4
A_51_P229599	<i>Etnk1</i>	ethanolamine kinase 1	1.0	2.0	1.6

**Table S4. 62 entities with lipid metabolic process out of the diabetes-dependent down-regulated entities**

Probe Name	Gene Symbol	Description	Fold Change		
			11w KKAy / 11w C57	11w KKAy / 4w KKAy	11w C57 / 4w C57
A_52_P483101	<i>Lpin1</i>	lipin 1	0.01	0.13	0.58
A_52_P483104	<i>Lpin1</i>	lipin 1	0.02	0.14	0.59
A_52_P483105	<i>Lpin1</i>	lipin 1	0.02	0.15	0.59
A_52_P557265	<i>Cyp39a1</i>	cytochrome P450, family 39, subfamily a, polypeptide 1	0.03	0.02	0.73
A_51_P515446	<i>Cyp39a1</i>	cytochrome P450, family 39, subfamily a, polypeptide 1	0.03	0.02	0.69
A_51_P394984	<i>Lpin1</i>	lipin 1	0.04	0.15	0.60
A_51_P355996	<i>Acot5</i>	acyl-CoA thioesterase 5	0.04	0.06	2.03
A_52_P472486	<i>Cyp2b10</i>	cytochrome P450, family 2, subfamily b, polypeptide 10	0.08	0.04	1.02
A_51_P182362	<i>Cyp2b10</i>	cytochrome P450, family 2, subfamily b, polypeptide 10	0.08	0.04	0.93
A_51_P493649	<i>Sult1e1</i>	sulfotransferase family 1E, member 1	0.11	0.11	1.36
A_52_P478025	<i>Smpd3</i>	sphingomyelin phosphodiesterase 3, neutral	0.13	0.24	1.38
A_51_P383459	<i>Smpd3</i>	sphingomyelin phosphodiesterase 3, neutral	0.17	0.28	0.97
A_52_P84027	<i>Cyp7a1</i>	cytochrome P450, family 7, subfamily a, polypeptide 1	0.18	0.23	0.86
A_52_P625508	<i>Cpt1b</i>	carnitine palmitoyltransferase 1b, muscle	0.19	0.19	1.31
A_51_P462918	<i>Ehhadh</i>	enoyl-Coenzyme A, hydratase/3-hydroxyacyl Coenzyme A dehydrogenase	0.21	0.33	1.30
A_51_P290981	<i>Cyp7a1</i>	cytochrome P450, family 7, subfamily a, polypeptide 1	0.21	0.31	0.96
A_52_P199905	<i>Slc27a1</i>	solute carrier family 27 (fatty acid transporter), member 1	0.24	0.38	1.26
A_52_P371922	<i>Dgkh</i>	diacylglycerol kinase, eta	0.25	0.35	0.59
A_52_P384069	<i>Gpcpd1</i>	glycerophosphocholine phosphodiesterase GDE1 homolog (S. cerevisiae)	0.27	0.30	0.74
A_51_P232913	<i>Cpt1b</i>	carnitine palmitoyltransferase 1b, muscle	0.28	0.24	1.45
A_51_P464791	<i>Gpcpd1</i>	glycerophosphocholine phosphodiesterase GDE1 homolog (S. cerevisiae)	0.32	0.31	0.72
A_52_P470017	<i>Gpcpd1</i>	glycerophosphocholine phosphodiesterase GDE1 homolog (S. cerevisiae)	0.32	0.32	0.68

**Table S4. Continued**

Probe Name	Gene Symbol	Description	Fold Change		
			11w KKAy / 11w C57	11w KKAy / 4w KKAy	11w C57 / 4w C57
A_52_P470017	<i>Gpcpd1</i>	glycerophosphocholine phosphodiesterase GDE1 homolog ( <i>S. cerevisiae</i> )	0.32	0.32	0.68
A_52_P113250	<i>Insig2</i>	insulin induced gene 2	0.33	0.44	1.09
A_51_P201709	<i>Ggt5</i>	gamma-glutamyltransferase 5	0.34	0.38	1.00
A_52_P537545	<i>Smpd3</i>	sphingomyelin phosphodiesterase 3, neutral	0.35	0.39	0.94
A_51_P327491	<i>Apoa4</i>	apolipoprotein A-IV	0.36	0.24	1.88
A_52_P681771	<i>Pnpla2</i>	patatin-like phospholipase domain containing 2	0.37	0.33	0.83
A_51_P197213	<i>Pnpla2</i>	patatin-like phospholipase domain containing 2	0.37	0.36	0.97
A_51_P451574	<i>Acot1</i>	acyl-CoA thioesterase 1	0.38	0.49	1.35
A_52_P525183	<i>Acot2</i>	acyl-CoA thioesterase 2	0.38	0.25	0.88
A_51_P439452	<i>Insig2</i>	insulin induced gene 2	0.39	0.50	1.26
A_52_P6588	<i>Cyp4a10</i>	cytochrome P450, family 4, subfamily a, polypeptide 10	0.39	0.35	1.02
A_52_P407755	<i>Gpcpd1</i>	glycerophosphocholine phosphodiesterase GDE1 homolog ( <i>S. cerevisiae</i> )	0.40	0.33	0.51
A_52_P219753	<i>Cpt1a</i>	carnitine palmitoyltransferase 1a, liver	0.41	0.46	0.87
A_51_P370438	<i>Lpin2</i>	lipin 2	0.42	0.35	0.93
A_51_P299287	<i>Impa2</i>	inositol (myo)-1(or 4)-monophosphatase 2	0.44	0.37	1.55
A_51_P137029	<i>Plce1</i>	phospholipase C, epsilon 1	0.45	0.38	1.09
A_52_P430523	<i>Cln8</i>	ceroid-lipofuscinosis, neuronal 8	0.46	0.49	1.05
A_52_P340136	<i>Cyp4a10</i>	cytochrome P450, family 4, subfamily a, polypeptide 10	0.48	0.49	1.17
A_51_P381618	<i>Pla1a</i>	phospholipase A1 member A	0.48	0.47	0.73
A_52_P257774	<i>Cyp4a10</i>	cytochrome P450, family 4, subfamily a, polypeptide 10	0.48	0.49	1.17
A_51_P481721	<i>Sult1d1</i>	sulfotransferase family 1D, member 1	0.49	0.41	1.11
A_51_P349341	<i>Npc1</i>	Niemann Pick type C1	0.50	0.46	0.94

**Table S4. Continued**

Probe Name	Gene Symbol	Description	Fold Change		
			11w KKAy / 11w C57	11w KKAy / 4w KKAy	11w C57 / 4w C57
A_51_P385598	<i>Slc37a4</i>	solute carrier family 37 (glucose-6-phosphate transporter), member 4	0.52	0.46	1.24
A_51_P192523	<i>Fgf23</i>	fibroblast growth factor 23	0.52	0.38	1.00
A_52_P431159	<i>Il1rn</i>	interleukin 1 receptor antagonist	0.53	0.23	0.67
A_51_P345649	<i>Pdgfra</i>	platelet derived growth factor receptor, alpha polypeptide	0.58	0.38	1.01
A_51_P132625	<i>Hsd17b11</i>	hydroxysteroid (17-beta) dehydrogenase 11	0.59	0.39	0.72
A_51_P321341	<i>Sult1a1</i>	sulfotransferase family 1A, phenol-preferring, member 1	0.60	0.50	0.90
A_51_P155755	<i>Pld6</i>	phospholipase D family, member 6	0.60	0.37	0.94
A_52_P402885	<i>Inpp1</i>	inositol polyphosphate-1-phosphatase	0.61	0.42	0.87
A_51_P422457	<i>Plcl1</i>	phospholipase C-like 1	0.63	0.42	0.77
A_52_P564544	<i>Fabp4</i>	fatty acid binding protein 4, adipocyte	0.64	0.41	0.67
A_51_P177762	<i>Rdh9</i>	retinol dehydrogenase 9	0.73	0.46	0.61
A_51_P336833	<i>Fabp4</i>	fatty acid binding protein 4, adipocyte	0.75	0.47	0.62
A_51_P336830	<i>Fabp4</i>	fatty acid binding protein 4, adipocyte	0.78	0.50	0.64
A_51_P374137	<i>Bcmo1</i>	beta-carotene 15,15'-monooxygenase	0.83	0.28	0.57
A_52_P564413	<i>Pik3c2g</i>	phosphatidylinositol 3-kinase, C2 domain containing, gamma polypeptide	0.88	0.33	0.87
A_52_P87843	<i>Aldh1a3</i>	aldehyde dehydrogenase family 1, subfamily A3	0.93	0.43	0.61
A_51_P500044	<i>Vldlr</i>	very low density lipoprotein receptor	1.06	0.29	0.54
A_51_P331737	<i>Acsm2</i>	acyl-CoA synthetase medium-chain family member 2	1.89	0.25	0.89
A_52_P500856	<i>Acsm2</i>	acyl-CoA synthetase medium-chain family member 2	2.22	0.26	0.77

**Table S5. Gene Ontology analysis of the differentially expressed genes between pre- and post-diabetic mice**

Entity list	GO terms
KKAy	lipid metabolic process
11w>4w, 526 entities	lipid biosynthetic process sterol metabolic process cellular lipid metabolic process negative regulation of lipid metabolic process organic acid metabolic process response to protein stimulus cellular ketone metabolic process regulation of cell adhesion negative regulation of cell adhesion
KKAy	M phase of mitotic cell cycle
11w<4w, 759 entities	nuclear division mitosis M phase organelle fission cell cycle process mitotic cell cycle cell cycle phase cell cycle phase lipid metabolic process

Gene Ontology (GO) analysis of the up- or down-regulated entities selected by comparison between 4w and 11w KKAy mice without the subtraction of age-dependent genes was carried out using DAVID. The top 10 functionally enriched GO terms ranked by p-value for GOTERM\_BP\_3 were shown.