

The Metabolic Syndrome and Microvascular Complications in a Murine Model of Type 2 Diabetes

Running title: Diabetic complications in *db/db* mice

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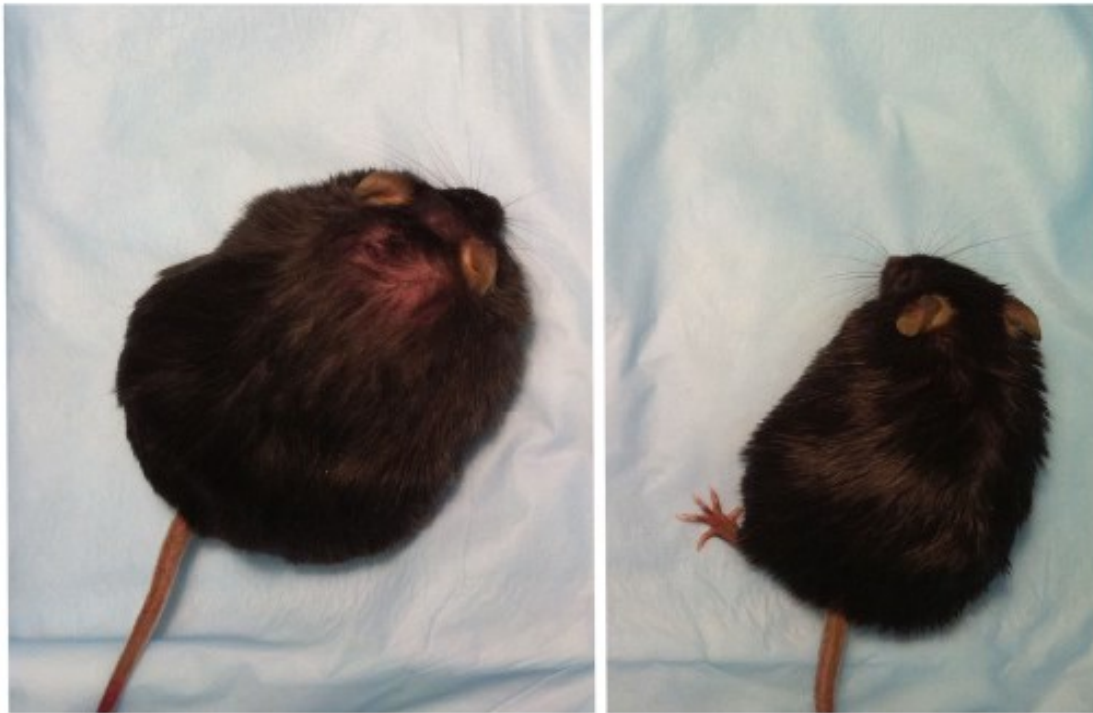
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SUPPLEMENTARY DATA

Supplementary Figure 1. Effects of pioglitazone on body weight. Representative images of the *db/db* mouse following 11wk of pioglitazone treatment (A) and untreated *db/db* mouse (B)

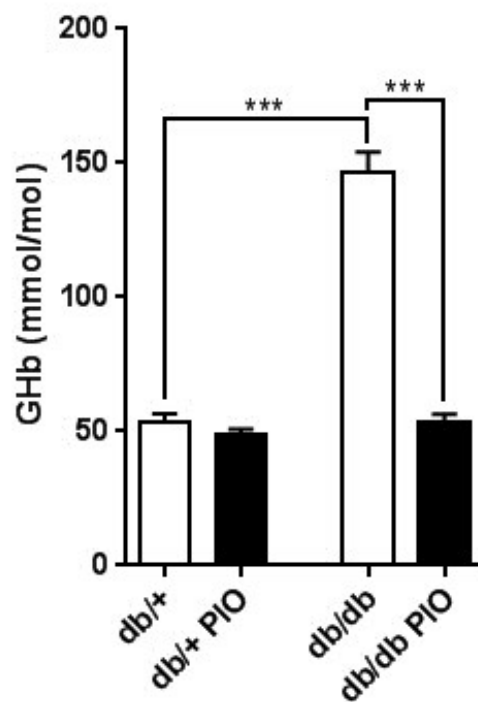


A. *db/db* PIO

B. *db/db*

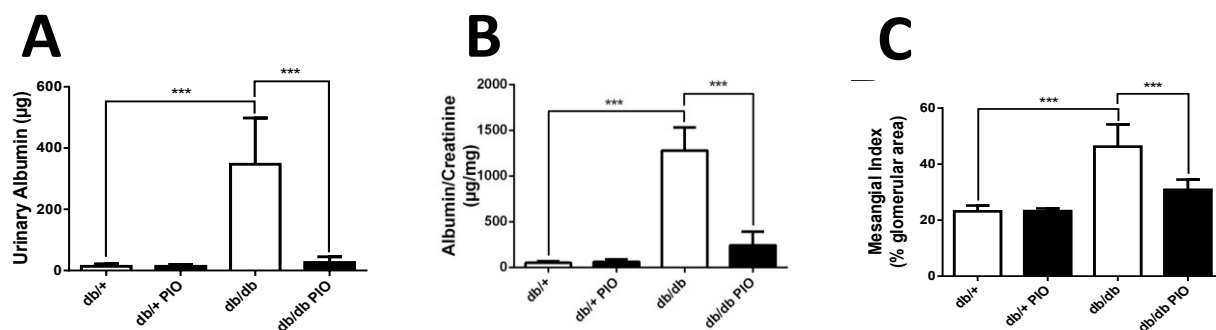
SUPPLEMENTARY DATA

Supplementary Figure 2. Effects of pioglitazone on GHb level in plasma. Following 11 weeks of pioglitazone treatment GHb (mmol/mol) was assessed. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. In all panels, $n = 6$.



SUPPLEMENTARY DATA

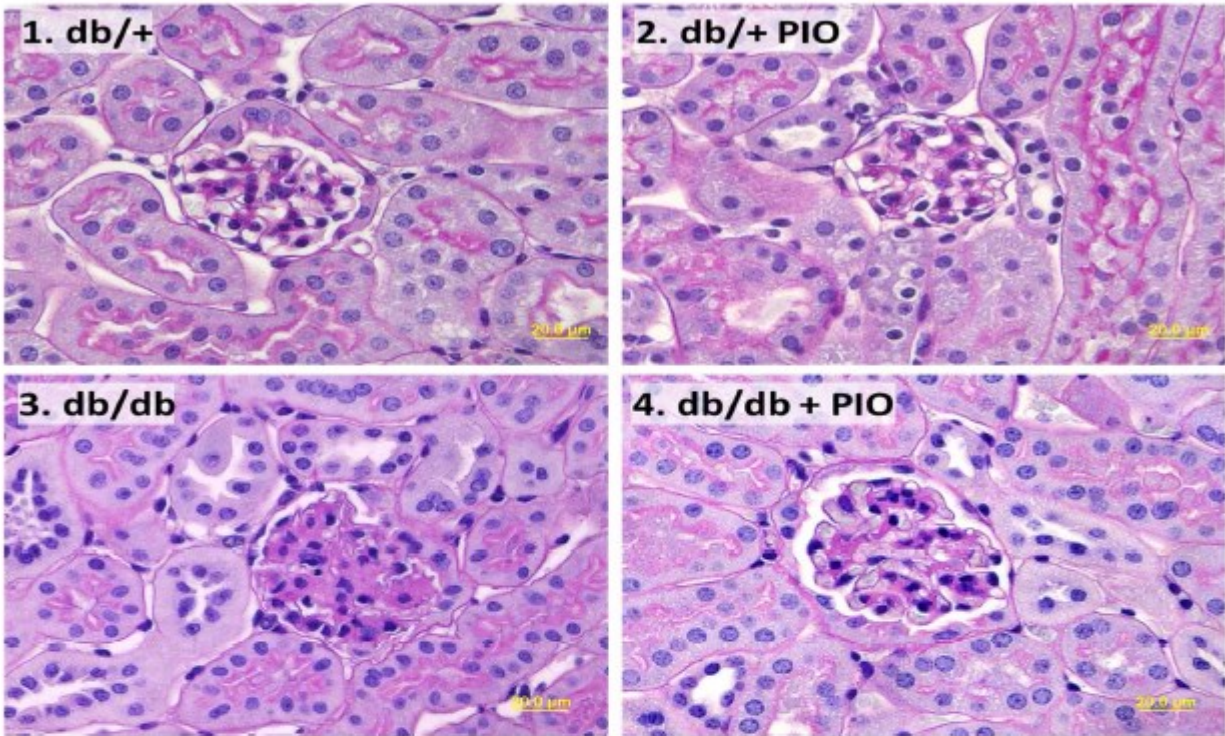
Supplementary Figure 3. Effects of pioglitazone on kidney function. Following 11 weeks of pioglitazone treatment, 24-hour urinary albumin excretion (A), albuminuria, based on albumin/creatinine ratios (ACRs) (B), and mesangial matrix accumulation (C) were assessed. *** $p < 0.001$. In all panels, $n = 6$.



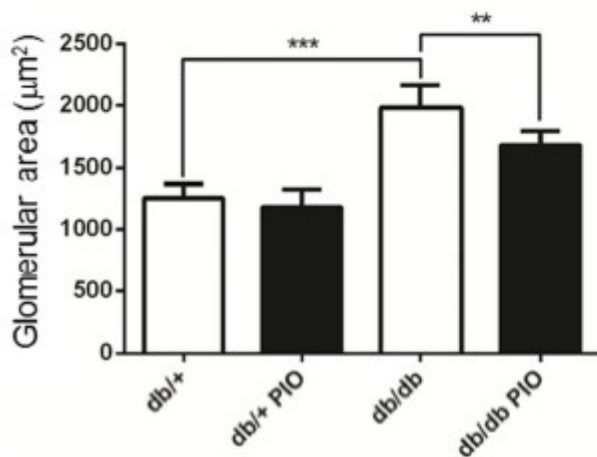
SUPPLEMENTARY DATA

Supplementary Figure 4. Effects on pioglitazone on diabetic glomerulopathy. Changes in glomerular matrix accumulation using a periodic acid Schiff (PAS) stain (A) for four animal groups (A1: *db/+*, A2: *db/+* PIO, A3: *db/db*, and A4: *db/db* PIO) and assessments of glomerular area (B) and glomerular PAS-positive area (C). ** $p < 0.01$; *** $p < 0.001$. In all groups, $n = 6$.

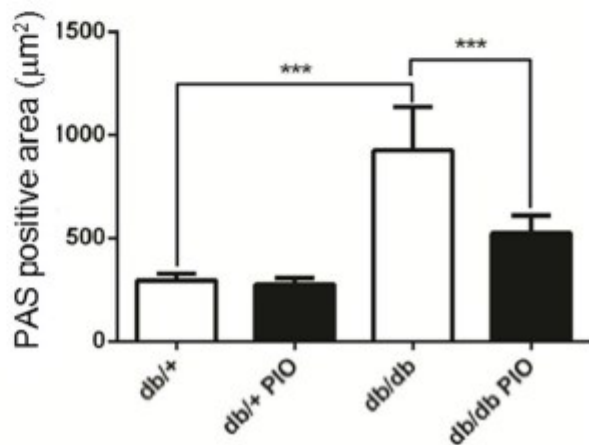
A



B



C



SUPPLEMENTARY DATA

Supplementary Table 1. List of primers used for validation of gene expression data by RT-qPCR. Primers were selected using PrimerBank (<http://pga.mgh.harvard.edu/primerbank/>) and purchased from Integrated DNA Technologies.

GeneID	Primer		Sequence	Fragment Size (bp)
93726	<i>Ear11</i>	Forward	TGGAGCAACTTGAGTCTCGAC	130
		Reverse	CGGGGATAGGCTCTGTTATAGA	
19017	<i>Ppargc1a</i>	Forward	CTGTATGGAGTGACATAGAGTGTGC	120
		Reverse	GAAAGCTGTCTGTATCCAAGTCATT	
216343	<i>Tph2</i>	Forward	TATGGAGCAGGGTACTTTCGT	126
		Reverse	GTCCTGAAAGGTGGTGATTAGG	
22227	<i>Ucp1</i>	Forward	AGGCTTCCAGTACCATTAGGT	133
		Reverse	CTGAGTGAGGCAAAGCTGATTT	

SUPPLEMENTARY DATA

Supplementary Table 2. Validation of microarray data using RT-PCR. Table indicates the fold change (FC) of DEGs, against Tyrosine 3-Monooxygenase/Tryptophan 5-Monooxygenase Activation (*Ywhaz*) gene as the endogenous control, from microarray that were selected for validation by RT-qPCR. *, p<0.05, ***, p<0.001

16 wk DEG	Symbol	Gene ID	Array (FC) <i>db/db</i> vs. <i>db/db</i> PIO	qPCR (FC) <i>db/db</i> vs. <i>db/db</i> PIO
uncoupling protein 1 (mitochondrial, proton carrier)	<i>UCP1</i>	22227	8.75	3.80***
acetyl-Coenzyme A acyltransferase 1B	<i>Acaa1b</i>	235674	2.43	1.11
cell death-inducing DNA fragmentation factor, alpha subunit-like effector A	<i>Cidea</i>	12683	1.95	2.51*
peroxisome proliferative activated receptor, gamma, coactivator 1 alpha	<i>Ppargc1a</i>	19017	1.23	1.05

SUPPLEMENTARY DATA

Supplementary Table 3. The overlap summary of the four DRG DEG sets in Figure 5A. The numbers in each cell follow the "A (B | C)" format, where A is the number of common DEGs, B is the number of common DEGs with the same direction of change, and C is the number of DEGs with opposite direction of change.

DEG Sets		<i>db/+ vs db/+</i> PIO	<i>db/+ vs db/db</i>	<i>db/+</i> PIO vs <i>db/db</i> PIO	<i>db/db vs db/db</i> PIO
	# DEGs	24	2082	2478	1811
<i>db/+ vs db/+</i> PIO	24	24 (24 0)	12 (12 0)	6 (4 2)	4 (4 0)
<i>db/+ vs db/db</i>	2082	12 (12 0)	2082 (2082 0)	804 (758 46)	455 (116 339)
<i>db/+</i> PIO vs <i>db/db</i> PIO	2478	6 (4 2)	804 (758 46)	2478 (2478 0)	802 (784 18)
<i>db/db vs db/db</i> PIO	1811	4 (4 0)	455 (116 339)	802 (784 18)	1811 (1811 0)

SUPPLEMENTARY DATA

Supplementary Table 4. The 20 most up-regulated genes and 20 most down-regulated genes that are dysregulated by diabetes and reversed by pioglitazone treatment in DRG. FC: fold-change; FDR: false discovery rate. Color indicates the up (red) or down (blue) regulation in the second group (eg. *db/db* in the *db/+* vs *db/db* comparison)

GeneID	Symbol	Description	<i>db/+</i> vs <i>db/db</i>		<i>db/db</i> vs <i>db/db</i> PIO	
			FC	FDR	FC	FDR
12655	Chi3l3	chitinase 3-like 3	5.36	4.7E-04	-2.66	9.6E-03
11656	Alas2	aminolevulinic acid synthase 2, erythroid	3.74	8.1E-03	-3.68	2.1E-02
268885	Stfa2l1	stefin A2 like 1	3.62	1.5E-04	-2.22	1.4E-02
213002	Ifitm6	interferon induced transmembrane protein 6	3.28	6.9E-04	-3.01	3.5E-03
17394	Mmp8	matrix metalloproteinase 8	2.92	2.5E-03	-3.25	4.1E-03
68891	Cd177	CD177 antigen	2.91	2.2E-03	-2.91	9.3E-03
12765	Cxcr2	chemokine (C-X-C motif) receptor 2	2.78	9.6E-03	-2.87	8.7E-03
17523	Mpo	myeloperoxidase	2.71	5.9E-03	-2.44	2.0E-02
13586	Ear1	eosinophil-associated, ribonuclease A family, member 1	2.61	2.6E-02	-3.50	2.1E-02
14289	Fpr2	formyl peptide receptor 2	2.59	5.9E-04	-2.53	3.4E-03
11813	Apoc2	apolipoprotein C-II	2.54	2.9E-05	-1.48	8.5E-03
15439	Hp	haptoglobin	2.47	5.5E-04	-1.58	4.0E-02
13035	Ctsg	cathepsin G	2.46	8.4E-03	-2.07	3.9E-02
16819	Lcn2	lipocalin 2	2.31	2.5E-03	-2.38	7.0E-03
17002	Ltf	lactotransferrin	2.21	9.1E-03	-3.37	3.4E-03
20305	Ccl6	chemokine (C-C motif) ligand 6	2.16	2.5E-03	-1.55	2.2E-02
69189	1810033B17Rik	RIKEN cDNA 1810033B17 gene	2.14	1.3E-02	-2.65	6.2E-03
66107	1100001G20Rik	RIKEN cDNA 1100001G20 gene	2.14	1.3E-02	-2.78	2.9E-03
14293	Fpr1	formyl peptide receptor 1	2.10	2.1E-02	-2.32	2.2E-02
17395	Mmp9	matrix metalloproteinase 9	2.03	7.4E-03	-2.18	1.1E-02
71354	Wdr31	WD repeat domain 31	-1.28	3.0E-02	1.34	2.8E-02
20600	Smr2	submaxillary gland androgen regulated protein 2	-1.28	4.3E-02	1.32	7.0E-03
233066	Syne4	expressed sequence AI428936	-1.28	8.1E-03	1.16	1.8E-02
17873	Gadd45b	growth arrest and DNA-damage-inducible 45 beta	-1.28	3.9E-04	1.11	4.1E-02
233040	Fbxo27	F-box protein 27	-1.29	2.9E-03	1.18	1.4E-02
67188	2700046G09Rik	RIKEN cDNA 2700046G09 gene	-1.29	7.9E-03	1.30	5.7E-03

SUPPLEMENTARY DATA

GeneID	Symbol	Description	<i>db/+ vs db/db</i>		<i>db/db vs db/db PIO</i>	
			FC	FDR	FC	FDR
100503092	Gm19550	hypothetical LOC100503092	-1.30	1.1E-03	1.14	3.8E-02
69358	Lrrc51	leucine rich repeat containing 51	-1.30	2.8E-03	1.14	3.5E-02
170458	Gpha2	glycoprotein hormone alpha 2	-1.31	1.9E-02	1.37	1.3E-02
66120	Fkbp11	FK506 binding protein 11	-1.32	6.0E-03	1.19	4.2E-02
212390	Klhl32	kelch-like 32 (Drosophila)	-1.34	1.8E-03	1.19	2.9E-02
237625	Pla2g3	phospholipase A2, group III	-1.35	2.2E-03	1.27	8.3E-03
67119	Ccdc159	coiled-coil domain containing 159	-1.38	2.3E-03	1.16	4.1E-02
75579	2310034G01Rik	RIKEN cDNA 2310034G01 gene	-1.39	1.6E-02	1.31	2.3E-02
104362	Meig1	meiosis expressed gene 1	-1.43	4.0E-03	1.23	2.4E-02
235330	Ttc12	tetratricopeptide repeat domain 12	-1.43	2.3E-04	1.19	1.8E-02
27274	Zfp354b	zinc finger protein 354B	-1.45	1.6E-02	1.30	4.4E-02
28240	Trpm2	transient receptor potential cation channel, subfamily M, member 2	-1.45	1.6E-03	1.17	3.3E-02
140743	Rem2	rad and gem related GTP binding protein 2	-1.48	3.9E-05	1.25	8.5E-03
232146	Eva1a	family with sequence similarity 176, member A	-1.50	3.4E-03	1.33	1.8E-02

SUPPLEMENTARY DATA

Supplementary Table 5. The 20 most up-regulated genes and 20 most down-regulated genes that are dysregulated by diabetes and exacerbated by pioglitazone treatment in DRG. FC: fold-change; FDR: false discovery rate. Color indicates the up (red) or down (blue) regulation in the second group (eg. *db/db* in the *db/+* vs *db/db* comparison)

GeneID	Symbol	Description	<i>db/+</i> vs <i>db/db</i>		<i>db/db</i> vs <i>db/db</i> PIO	
			FC	FDR	FC	FDR
71760	Agxt2l1	alanine-glyoxylate aminotransferase 2-like 1	3.80	2.9E-05	1.47	8.2E-03
12491	Cd36	CD36 antigen	2.30	2.4E-03	2.53	1.0E-02
11450	Adipoq	adiponectin, C1Q and collagen domain containing	2.21	3.8E-02	4.18	6.4E-03
16846	Lep	leptin	1.88	2.6E-02	4.86	4.9E-03
71406	5430416O09Rik	RIKEN cDNA 5430416O09 gene	1.87	6.0E-04	1.36	3.0E-02
70358	Steap1	six transmembrane epithelial antigen of the prostate 1	1.60	5.6E-03	1.31	2.1E-02
230379	Acer2	alkaline ceramidase 2	1.47	1.6E-02	1.68	2.6E-03
54153	Rasa4	RAS p21 protein activator 4	1.38	2.7E-04	1.17	9.3E-03
207798	Gramd1c	GRAM domain containing 1C	1.36	2.8E-03	1.39	1.3E-03
68453	Gpihbp1	GPI-anchored HDL-binding protein 1	1.36	3.9E-02	1.61	3.4E-03
75180	4930538K18Rik	RIKEN cDNA 4930538K18 gene	1.34	3.0E-02	1.42	4.7E-02
237246	BC022960	cDNA sequence BC022960	1.31	1.2E-02	1.35	2.2E-02
78751	Zc3h6	zinc finger CCCH type containing 6	1.30	4.1E-02	1.41	4.3E-03
16890	Lipe	lipase, hormone sensitive	1.30	4.8E-02	1.85	2.4E-02
56448	Cyp2d22	cytochrome P450, family 2, subfamily d, polypeptide 22	1.30	3.7E-03	1.30	4.5E-03
53608	Map3k6	mitogen-activated protein kinase kinase kinase 6	1.29	7.9E-03	1.19	3.0E-02
20514	Slc1a5	solute carrier family 1 (neutral amino acid transporter), member 5	1.29	9.7E-03	1.19	4.7E-02
269630	5031425E22Rik	RIKEN cDNA 5031425E22 gene	1.26	3.4E-02	1.24	2.6E-02
73001	2900055J20Rik	RIKEN cDNA 2900055J20 gene	1.25	2.4E-03	1.48	4.0E-03
216233	Socs2	suppressor of cytokine signaling 2	1.25	2.5E-03	1.16	2.4E-02
230235	Frrs1l	RIKEN cDNA 6430704M03 gene	-1.22	1.3E-02	-1.17	4.5E-02
16416	Itgb3	integrin beta 3	-1.22	2.2E-02	-1.49	1.3E-02
378462	Morn2	MORN repeat containing 2	-1.22	1.0E-03	-1.10	3.0E-02
12168	Bmpr2	bone morphogenic protein receptor, type II (serine/threonine kinase)	-1.22	2.0E-02	-1.15	3.5E-02
12443	Ccnd1	cyclin D1	-1.22	9.5E-04	-1.33	4.6E-04
234700	Nrn1l	neuritin 1-like	-1.23	4.3E-03	-1.15	3.4E-02

SUPPLEMENTARY DATA

GeneID	Symbol	Description	<i>db/+ vs db/db</i>		<i>db/db vs db/db PIO</i>	
			FC	FDR	FC	FDR
22027	Hsp90b1	heat shock protein 90, beta (Grp94), member 1	-1.23	9.4E-04	-1.17	3.1E-03
70356	St13	suppression of tumorigenicity 13	-1.24	8.9E-03	-1.24	1.4E-02
15505	Hsph1	heat shock 105kDa/110kDa protein 1	-1.24	4.9E-04	-1.21	2.6E-03
12140	Fabp7	fatty acid binding protein 7, brain	-1.24	3.8E-03	-1.42	1.3E-02
216166	Plk5	polo-like kinase 5 (Drosophila)	-1.29	1.2E-02	-1.31	1.4E-02
106869	Tnfaip8	tumor necrosis factor, alpha-induced protein 8	-1.34	6.3E-03	-1.40	1.8E-02
16840	Lect1	leukocyte cell derived chemotaxin 1	-1.34	2.2E-04	-1.13	2.8E-02
384061	Fndc5	fibronectin type III domain containing 5	-1.39	2.5E-04	-1.12	4.3E-02
18451	P4ha1	procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), alpha 1 polypeptide	-1.46	9.1E-04	-1.30	2.8E-02
170813	Ms4a3	membrane-spanning 4-domains, subfamily A, member 3	-1.47	2.7E-03	-1.46	8.4E-03
12406	Serpinh1	serine (or cysteine) peptidase inhibitor, clade H, member 1	-1.53	8.4E-03	-1.88	2.0E-03
71111	Gpr39	G protein-coupled receptor 39	-1.57	6.9E-03	-1.37	5.0E-03
20290	Ccl1	chemokine (C-C motif) ligand 1	-1.61	9.0E-04	-1.26	4.3E-02
72585	Lypd1	Ly6/Plaur domain containing 1	-1.62	1.5E-03	-1.32	2.9E-03

SUPPLEMENTARY DATA

Supplementary Table 6. The 20 most up-regulated genes and 20 most down-regulated genes that are dysregulated only by diabetes (*db/+* vs *db/db*) and not by pioglitazone treatment in DRG. FC: fold-change; FDR: false discovery rate.

GeneID	Symbol	Description	FC	FDR
16017	Ighg1	immunoglobulin heavy constant gamma 1 (G1m marker)	4.08	1.8E-02
16016	Ighg2b	immunoglobulin heavy constant gamma 2B	3.91	8.7E-04
20533	Slc4a1	solute carrier family 4 (anion exchanger), member 1	3.11	8.9E-03
13034	Ctse	cathepsin E	2.88	6.4E-03
57435	Plin4	perilipin 4	2.86	1.4E-03
14934	Gypa	glycophorin A	2.84	4.1E-02
234421	Cib3	calcium and integrin binding family member 3	2.54	7.7E-05
20863	Stfa3	stefin A3	2.51	4.1E-03
14063	F2rl1	coagulation factor II (thrombin) receptor-like 1	2.46	2.9E-05
110595	Timp4	tissue inhibitor of metalloproteinase 4	2.29	1.1E-02
19824	Trim10	tripartite motif-containing 10	2.28	2.5E-02
100503518	Gm11827	hypothetical LOC100503518	2.24	1.0E-02
16997	Ltbp2	latent transforming growth factor beta binding protein 2	2.16	2.9E-05
14460	Gata1	GATA binding protein 1	2.13	1.3E-02
18405	Orm1	orosomuroid 1	2.06	3.5E-03
21349	Tal1	T-cell acute lymphocytic leukemia 1	2.01	1.7E-02
213068	Tmem71	transmembrane protein 71	1.95	1.3E-02
20284	Scrg1	scrapie responsive gene 1	1.84	1.6E-02
74720	Cldn26	transmembrane protein 114	1.79	2.3E-04
93671	Cd163	CD163 antigen	1.77	3.1E-03
71412	Dhrs2	dehydrogenase/reductase member 2	-1.58	1.0E-04
99899	Ifi44	interferon-induced protein 44	-1.61	2.7E-03
99571	Fgg	fibrinogen gamma chain	-1.65	4.7E-03
12970	Crygs	crystallin, gamma S	-1.68	9.5E-04
193740	Hspa1a	heat shock protein 1A	-1.68	9.8E-03
219132	Phf11d	DNA segment, Chr 14, ERATO Doi 668, expressed	-1.68	5.3E-03
24110	Usp18	ubiquitin specific peptidase 18	-1.68	5.6E-03
85030	Tnfrsf25	tumor necrosis factor receptor superfamily, member 25	-1.70	1.3E-02

SUPPLEMENTARY DATA

GeneID	Symbol	Description	FC	FDR
58807	Slco1c1	solute carrier organic anion transporter family, member 1c1	-1.72	1.2E-04
107146	Glyat	glycine-N-acyltransferase	-1.78	1.3E-02
210463	Slc22a22	cDNA sequence BC026439	-1.79	5.1E-04
246048	Chodl	chondrolectin	-1.80	3.6E-03
97114	Hist2h3c2	histone cluster 2, H3c2, pseudogene	-1.80	2.9E-05
229550	9130204L05Rik	RIKEN cDNA 9130204L05 gene	-1.84	2.0E-02
16019	Ighm	immunoglobulin heavy chain 6 (heavy chain of IgM)	-1.84	5.0E-03
18857	Pmp2	peripheral myelin protein 2	-1.97	3.5E-03
74748	Slamf8	SLAM family member 8	-1.97	3.2E-02
57262	Retnla	resistin like alpha	-2.14	2.0E-02
66198	Them5	thioesterase superfamily member 5	-2.16	1.2E-04
109254	Adtrp	RIKEN cDNA 9530008L14 gene	-2.45	5.5E-04

SUPPLEMENTARY DATA

Supplementary Table 7. The 20 most up-regulated genes and 20 most down-regulated genes that are dysregulated only by pioglitazone treatment (*db/db* vs *db/db* PIO) and not by diabetes (*db/+* vs *db/db*) in DRG. FC: fold-change; FDR: false discovery rate.

GeneID	Symbol	Description	FC	FDR
22227	Ucp1	uncoupling protein 1 (mitochondrial, proton carrier)	8.75	4.3E-03
14311	Cidec	cell death-inducing DFFA-like effector c	6.86	1.3E-03
11770	Fabp4	fatty acid binding protein 4, adipocyte	5.10	5.6E-04
93726	Ear11	eosinophil-associated, ribonuclease A family, member 11	4.85	6.6E-04
13106	Cyp2e1	cytochrome P450, family 2, subfamily e, polypeptide 1	4.64	6.5E-03
24108	Ubd	ubiquitin D	4.03	3.4E-03
63954	Rbp7	retinol binding protein 7, cellular	2.96	1.9E-04
246747	Adig	adipogenin	2.95	1.2E-03
16956	Lpl	lipoprotein lipase	2.91	3.9E-03
57264	Retn	resistin	2.49	6.8E-03
235674	Acaa1b	acetyl-Coenzyme A acyltransferase 1B	2.43	6.2E-03
13850	Ephx2	epoxide hydrolase 2, cytoplasmic	2.11	3.4E-03
71939	Apo16	apolipoprotein L 6	2.07	4.1E-02
58805	Mlxipl	MLX interacting protein-like	1.98	4.0E-02
12683	Cidea	cell death-inducing DNA fragmentation factor, alpha subunit-like effector A	1.95	9.5E-03
18113	Nnmt	nicotinamide N-methyltransferase	1.91	4.1E-02
232493	Gys2	glycogen synthase 2	1.85	2.6E-02
13120	Cyp4b1	cytochrome P450, family 4, subfamily b, polypeptide 1	1.84	5.4E-03
240239	Gpr151	G protein-coupled receptor 151	1.79	4.8E-02
22690	Zfp28	zinc finger protein 28	1.67	6.7E-04
11537	Cfd	complement factor D (adipsin)	-1.86	4.8E-02
60361	Ms4a4b	membrane-spanning 4-domains, subfamily A, member 4B	-1.91	6.4E-03
15985	Cd79b	CD79B antigen	-1.92	5.4E-03
14960	H2-Aa	histocompatibility 2, class II antigen A, alpha	-1.93	2.6E-03
227929	Cytip	cytohesin 1 interacting protein	-1.93	2.6E-03
20345	Selplg	selectin, platelet (p-selectin) ligand	-1.94	1.4E-02
100504404	H2-Ea-ps	h-2 class II histocompatibility antigen, E-K alpha chain-like	-2.04	2.6E-03
21973	Top2a	topoisomerase (DNA) II alpha	-2.08	8.0E-03

SUPPLEMENTARY DATA

GeneID	Symbol	Description	FC	FDR
50706	Postn	periostin, osteoblast specific factor	-2.09	5.0E-04
14969	H2-Eb1	histocompatibility 2, class II antigen E beta	-2.11	2.6E-03
11687	Alox15	arachidonate 15-lipoxygenase	-2.18	3.4E-02
16071	Igkc	immunoglobulin kappa chain, constant region	-2.28	2.1E-02
23833	Cd52	CD52 antigen	-2.43	1.3E-03
53856	Prg3	proteoglycan 3	-2.46	3.3E-02
64380	Ms4a4c	membrane-spanning 4-domains, subfamily A, member 4C	-2.64	1.3E-03
231507	Plac8	placenta-specific 8	-2.66	1.8E-03
13861	Epx	eosinophil peroxidase	-2.69	3.0E-02
20343	Sell	selectin, lymphocyte	-2.74	5.5E-03
328563	Apol11b	apolipoprotein L 11b	-2.83	8.5E-03
20558	Sifn4	schlafen 4	-3.36	7.1E-04

SUPPLEMENTARY DATA

Supplementary Table 8. The overlap summary of four SCN DEG sets in Figure 6A. The numbers in each cell follow the "A (B | C)" format, where A is the number of common DEGs, B is the number of common DEGs with the same direction of change, and C is the number of DEGs with opposite direction of change.

DEG Sets		<i>db/+ vs db/+ PIO</i>	<i>db/+ vs db/db</i>	<i>db/+ PIO vs db/db PIO</i>	<i>db/db vs db/db PIO</i>
	# DEGs	1182	1066	2596	4537
<i>db/+ vs db/+ PIO</i>	1182	1182 (1182 0)	187 (149 38)	374 (308 66)	872 (867 5)
<i>db/+ vs db/db</i>	1066	187 (149 38)	1066 (1066 0)	452 (436 16)	484 (161 323)
<i>db/+ PIO vs db/db PIO</i>	2596	374 (308 66)	452 (436 16)	2596 (2596 0)	1600 (1559 41)
<i>db/db vs db/db PIO</i>	4537	872 (867 5)	484 (161 323)	1600 (1559 41)	4537 (4537 0)

SUPPLEMENTARY DATA

Supplementary Table 9. The 20 most up-regulated genes and 20 most down-regulated genes that are dysregulated by diabetes and reversed by pioglitazone treatment in SCN. FC: fold-change; FDR: false discovery rate. Color indicates the up (red) or down (blue) regulation in the second group (eg. *db/db* in the *db/+* vs *db/db* comparison)

GeneID	Symbol	Description	<i>db/+</i> vs <i>db/db</i>		<i>db/db</i> vs <i>db/db</i> PIO	
			FC	FDR	FC	FDR
20284	Scrg1	scrapie responsive gene 1	3.17	7.9E-03	-1.88	1.9E-02
240332	Slc6a7	solute carrier family 6 (neurotransmitter transporter, L-proline), member 7	3.07	1.7E-06	-2.53	2.3E-06
24111	Uts2	urotensin 2	3.01	8.0E-05	-1.58	5.9E-03
58222	Rab37	RAB37, member of RAS oncogene family	2.50	1.5E-04	-1.61	7.1E-03
66526	Tceanc2	RIKEN cDNA 2210012G02 gene	2.50	2.0E-02	-2.13	2.7E-02
223920	Soat2	sterol O-acyltransferase 2	2.48	9.1E-04	-2.04	5.4E-04
21956	Tnnt2	troponin T2, cardiac	2.33	1.1E-03	-1.35	3.3E-02
11685	Alox12e	arachidonate lipoxygenase, epidermal	2.30	1.4E-04	-1.84	8.4E-04
18039	Nefl	neurofilament, light polypeptide	2.17	4.9E-04	-2.10	2.9E-04
66809	Krt20	keratin 20	2.11	2.1E-03	-1.42	2.5E-02
381319	Batf3	basic leucine zipper transcription factor, ATF-like 3	2.10	5.4E-04	-1.51	8.0E-04
12659	Ovgp1	oviductal glycoprotein 1	2.10	4.4E-04	-1.33	3.5E-02
11601	Angpt2	angiopoietin 2	2.07	4.0E-03	-1.78	2.7E-04
56747	Sez6l	seizure related 6 homolog like	2.06	5.0E-03	-1.62	2.3E-02
76640	1700113H08Rik	RIKEN cDNA 1700113H08 gene	2.00	1.5E-02	-1.72	4.7E-03
70571	Tcerg1l	transcription elongation regulator 1-like	1.99	1.5E-02	-2.09	3.5E-03
235048	Zfp599	zinc finger protein 599	1.95	3.3E-02	-2.01	2.2E-03
22360	Nrsn1	neurensin 1	1.95	1.1E-02	-1.61	5.6E-03
11830	Aqp5	aquaporin 5	1.92	1.3E-02	-2.92	4.0E-05
230678	Tmem125	transmembrane protein 125	1.89	2.6E-03	-1.86	7.5E-04
17329	Cxcl9	chemokine (C-X-C motif) ligand 9	-1.99	2.5E-02	11.06	8.6E-04
58805	Mlxipl	MLX interacting protein-like	-2.01	3.5E-02	3.37	9.6E-05
20528	Slc2a4	solute carrier family 2 (facilitated glucose transporter), member 4	-2.02	7.8E-03	3.51	8.2E-06
171180	Syt12	synaptotagmin XII	-2.06	4.1E-02	2.83	1.8E-05
22117	Tst	thiosulfate sulfurtransferase, mitochondrial	-2.08	1.4E-04	2.19	1.2E-05
58200	Ppp1r1a	protein phosphatase 1, regulatory (inhibitor) subunit 1A	-2.19	2.3E-03	8.21	3.2E-07

SUPPLEMENTARY DATA

GeneID	Symbol	Description	<i>db/+ vs db/db</i>		<i>db/db vs db/db PIO</i>	
			FC	FDR	FC	FDR
21835	Thrsp	thyroid hormone responsive SPOT14 homolog (Rattus)	-2.28	1.5E-02	3.67	7.8E-06
104158	Ces1d	carboxylesterase 1D	-2.32	2.2E-02	2.95	1.7E-03
53311	Mybph	myosin binding protein H	-2.36	1.9E-03	1.77	2.6E-03
26464	Vnn3	vanin 3	-2.39	2.4E-02	2.23	3.7E-03
13106	Cyp2e1	cytochrome P450, family 2, subfamily e, polypeptide 1	-2.53	3.0E-04	3.28	8.2E-06
83961	Nrg4	neuregulin 4	-2.64	5.2E-03	4.77	2.5E-05
170786	Cd209a	CD209a antigen	-2.68	4.6E-03	1.79	4.8E-02
243270	Gpr81	G protein-coupled receptor 81	-2.77	4.1E-02	2.04	1.7E-02
12683	Cidea	cell death-inducing DNA fragmentation factor, alpha subunit-like effector A	-2.82	9.8E-03	71.60	2.5E-07
18534	Pck1	phosphoenolpyruvate carboxykinase 1, cytosolic	-3.07	1.5E-02	2.90	1.4E-03
234564	Ces1f	carboxylesterase 1F	-5.27	5.0E-03	7.16	8.5E-04
68393	Mogat1	monoacylglycerol O-acyltransferase 1	-5.47	8.0E-05	1.89	1.2E-03
20319	Sfrp2	secreted frizzled-related protein 2	-5.48	1.4E-04	3.73	1.1E-04
13107	Cyp2f2	cytochrome P450, family 2, subfamily f, polypeptide 2	-30.87	1.6E-10	3.63	6.4E-04

SUPPLEMENTARY DATA

Supplementary Table 10. The 20 most up-regulated genes and 20 most down-regulated genes that are dysregulated by diabetes and exacerbated by pioglitazone treatment in SCN. FC: fold-change; FDR: false discovery rate. Color indicates the up (red) or down (blue) regulation in the second group (eg. *db/db* in the *db/+* vs *db/db* comparison)

GeneID	Symbol	Description	<i>db/+</i> vs <i>db/db</i>		<i>db/db</i> vs <i>db/db</i> PIO	
			FC	FDR	FC	FDR
93726	Ear11	eosinophil-associated, ribonuclease A family, member 11	26.17	1.2E-03	7.96	4.2E-04
24108	Ubd	ubiquitin D	8.57	3.2E-03	6.22	4.6E-04
67717	Lipf	lipase, gastric	6.46	1.9E-02	4.74	1.6E-03
381974	Mrgprg	MAS-related GPR, member G	5.44	1.9E-03	2.63	6.1E-03
16009	Igfbp3	insulin-like growth factor binding protein 3	3.54	1.1E-04	1.38	2.2E-02
11425	Apoc4	apolipoprotein C-IV	3.35	1.9E-03	3.62	1.0E-04
11813	Apoc2	apolipoprotein C-II	3.25	9.5E-03	2.81	2.2E-03
433470	AA467197	expressed sequence AA467197	2.78	8.4E-03	5.28	4.0E-03
17896	Myl4	myosin, light polypeptide 4	2.17	7.3E-03	1.93	1.7E-03
16846	Lep	leptin	2.15	8.2E-03	1.44	1.8E-02
13723	Emb	embigin	2.14	3.2E-02	1.85	1.7E-02
213696	Duoxa1	dual oxidase maturation factor 1	2.04	1.2E-03	1.99	6.7E-05
21857	Timp1	tissue inhibitor of metalloproteinase 1	1.89	1.6E-02	2.13	4.8E-02
21906	Otop1	otopetrin 1	1.85	7.3E-03	1.87	1.6E-03
20753	Sprr1a	small proline-rich protein 1A	1.80	2.6E-02	2.70	8.0E-03
15484	Hsd11b2	hydroxysteroid 11-beta dehydrogenase 2	1.80	9.9E-03	1.43	3.6E-02
14168	Fgf13	fibroblast growth factor 13	1.77	1.5E-02	2.75	4.8E-05
68453	Gpihbp1	GPI-anchored HDL-binding protein 1	1.73	1.1E-02	1.87	2.5E-04
12534	Cdk1	cyclin-dependent kinase 1	1.72	4.3E-02	1.71	2.2E-02
232599	Gm4876	predicted gene 4876	1.65	1.0E-02	1.48	4.9E-02
14706	Gng4	guanine nucleotide binding protein (G protein), gamma 4	-1.64	4.6E-03	-1.47	2.2E-02
72324	Plxdc1	plexin domain containing 1	-1.65	8.2E-03	-1.93	2.1E-04
384009	Glipr2	GLI pathogenesis-related 2	-1.65	1.4E-02	-1.32	4.6E-02
19275	Ptprn	protein tyrosine phosphatase, receptor type, N	-1.73	5.9E-03	-1.39	2.5E-02
12578	Cdkn2a	cyclin-dependent kinase inhibitor 2A	-1.75	8.0E-03	-1.68	4.7E-03
244654	Mtss1l	metastasis suppressor 1-like	-1.80	1.3E-02	-1.60	3.5E-02

SUPPLEMENTARY DATA

GeneID	Symbol	Description	<i>db/+ vs db/db</i>		<i>db/db vs db/db PIO</i>	
			FC	FDR	FC	FDR
11514	Adcy8	adenylate cyclase 8	-1.80	6.2E-03	-2.00	2.2E-03
11537	Cfd	complement factor D (adipsin)	-1.81	6.3E-04	-1.65	2.1E-03
170741	Pilrb1	paired immunoglobulin-like type 2 receptor beta 1	-1.89	1.9E-02	-1.95	4.3E-04
64082	Popdc2	popeye domain containing 2	-1.90	1.1E-02	-1.63	3.5E-02
104885	Tmem179	transmembrane protein 179	-1.92	8.3E-03	-2.02	2.4E-05
80891	Fcrls	Fc receptor-like 5, scavenger receptor	-1.99	1.5E-03	-2.10	7.7E-05
19242	Ptn	pleiotrophin	-2.12	1.2E-02	-1.78	1.4E-03
13138	Dag1	dystroglycan 1	-2.21	4.4E-02	-1.62	1.3E-03
66198	Them5	thioesterase superfamily member 5	-2.21	1.1E-04	-1.69	3.8E-03
12970	Crygs	crystallin, gamma S	-2.31	4.6E-03	-1.63	1.6E-02
20983	Syt4	synaptotagmin IV	-2.79	1.1E-04	-1.50	1.3E-02
12824	Col2a1	collagen, type II, alpha 1	-2.89	5.0E-04	-3.49	3.1E-05
17395	Mmp9	matrix metalloproteinase 9	-3.45	2.1E-04	-1.61	2.6E-02
18979	Pon1	paraoxonase 1	-16.82	4.1E-08	-2.57	1.3E-03

SUPPLEMENTARY DATA

Supplementary Table 11. The 20 most up-regulated genes and 20 most down-regulated genes that are dysregulated only by diabetes (*db/+* vs *db/db*) and not by pioglitazone treatment in SCN. FC: fold-change; FDR: false discovery rate.

GeneID	Symbol	Description	FC	FDR
17381	Mmp12	matrix metalloproteinase 12	44.77	1.3E-04
216343	Tph2	tryptophan hydroxylase 2	11.70	1.1E-03
16411	Itgax	integrin alpha X	9.52	8.3E-04
242341	Atp6v0d2	ATPase, H ⁺ transporting, lysosomal V0 subunit D2	9.13	5.5E-04
71760	Agxt2l1	alanine-glyoxylate aminotransferase 2-like 1	6.39	4.1E-08
14068	F7	coagulation factor VII	6.10	3.3E-03
16197	Il7r	interleukin 7 receptor	6.00	1.8E-03
17474	Clec4d	C-type lectin domain family 4, member d	5.28	3.6E-03
11501	Adam8	a disintegrin and metalloproteinase domain 8	5.24	2.1E-03
18430	Oxtr	oxytocin receptor	5.11	5.0E-04
232680	Cpa2	carboxypeptidase A2, pancreatic	4.97	9.5E-03
75766	Dcstamp	transmembrane 7 superfamily member 4	4.33	7.5E-03
50778	Rgs1	regulator of G-protein signaling 1	4.14	1.4E-02
50765	Tfr2	transferrin receptor 2	4.08	2.3E-03
12309	S100g	S100 calcium binding protein G	3.84	6.5E-04
12523	Cd84	CD84 antigen	3.84	7.8E-03
278180	Vsig4	V-set and immunoglobulin domain containing 4	3.35	8.2E-03
234421	Cib3	calcium and integrin binding family member 3	3.27	1.4E-04
56857	Slc37a2	solute carrier family 37 (glycerol-3-phosphate transporter), member 2	3.21	8.3E-04
109648	Npy	neuropeptide Y	3.09	2.1E-03
13003	Vcan	versican	-1.95	3.5E-05
56811	Dkk2	dickkopf homolog 2 (<i>Xenopus laevis</i>)	-1.95	2.4E-02
57764	Ntn4	netrin 4	-1.96	1.8E-03
50786	Hs6st2	heparan sulfate 6-O-sulfotransferase 2	-1.98	2.1E-03
16005	Igfals	insulin-like growth factor binding protein, acid labile subunit	-2.04	3.4E-02
74342	Lrrtm1	leucine rich repeat transmembrane neuronal 1	-2.04	4.4E-03
24110	Usp18	ubiquitin specific peptidase 18	-2.08	4.8E-04
16668	Krt18	keratin 18	-2.11	2.4E-03

SUPPLEMENTARY DATA

GeneID	Symbol	Description	FC	FDR
319783	A730056A06Rik	RIKEN cDNA A730056A06 gene	-2.27	2.6E-02
233271	Luzp2	leucine zipper protein 2	-2.34	5.2E-03
19662	Rbp4	retinol binding protein 4, plasma	-2.35	2.5E-03
14172	Fgf18	fibroblast growth factor 18	-2.35	9.5E-03
11657	Alb	albumin	-2.44	1.5E-02
64661	Krtdap	keratinocyte differentiation associated protein	-2.58	3.0E-03
71412	Dhrs2	dehydrogenase/reductase member 2	-2.60	1.1E-04
330908	Opcml	opioid binding protein/cell adhesion molecule-like	-2.67	9.1E-04
56471	Stmn4	stathmin-like 4	-2.68	2.8E-03
69123	Eci3	RIKEN cDNA 1810022C23 gene	-2.81	3.4E-03
11556	Adrb3	adrenergic receptor, beta 3	-2.82	5.7E-03
16178	Il1r2	interleukin 1 receptor, type II	-2.96	7.8E-03

SUPPLEMENTARY DATA

Supplementary Table 12. The 20 most up-regulated genes and 20 most down-regulated genes that are dysregulated only by pioglitazone treatment (*db/db* vs *db/db* PIO) and not by diabetes (*db/+* vs *db/db*) in SCN. FC: fold-change; FDR: false discovery rate.

GeneID	Symbol	Description	FC	FDR
22227	Ucp1	uncoupling protein 1 (mitochondrial, proton carrier)	146.47	2.5E-08
12686	Elovl3	elongation of very long chain fatty acids (FEN1/Elo2, SUR4/Elo3, yeast)-like 3	125.66	4.2E-10
232493	Gys2	glycogen synthase 2	32.25	2.3E-08
67758	Aadac	arylacetamide deacetylase (esterase)	29.90	4.0E-08
228677	Sptlc3	serine palmitoyltransferase, long chain base subunit 3	27.72	2.2E-10
78977	Popdc3	popeye domain containing 3	26.71	2.6E-07
12869	Cox8b	cytochrome c oxidase, subunit VIIIb	16.95	2.0E-05
13088	Cyp2b10	cytochrome P450, family 2, subfamily b, polypeptide 10	15.33	7.9E-06
13004	Ncan	neurocan	11.07	3.8E-06
107146	Glyat	glycine-N-acyltransferase	10.66	9.4E-04
66968	Plin5	perilipin 5	10.01	3.4E-06
68172	Rpl39l	ribosomal protein L39-like	9.92	2.2E-03
11489	Adam12	a disintegrin and metallopeptidase domain 12 (meltrin alpha)	9.48	7.9E-07
268345	Kcnc2	potassium voltage gated channel, Shaw-related subfamily, member 2	9.25	2.8E-06
74121	Acox1	acyl-Coenzyme A oxidase-like	9.04	1.8E-06
108812	Als2cr12	amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 12 (human)	8.51	1.5E-05
109245	Lrrc39	leucine rich repeat containing 39	7.89	1.2E-05
108078	Olr1	oxidized low density lipoprotein (lectin-like) receptor 1	7.85	1.2E-04
105892	9030619P08Rik	RIKEN cDNA 9030619P08 gene	7.71	1.2E-06
75552	Paqr9	progesterin and adipoQ receptor family member IX	7.19	4.3E-06
56839	Lgi1	leucine-rich repeat LGI family, member 1	-2.36	1.3E-05
73720	Cst6	cystatin E/M	-2.45	5.3E-05
209966	Pgbd5	piggyBac transposable element derived 5	-2.46	8.6E-05
140703	Emid1	EMI domain containing 1	-2.46	1.7E-05
64385	Cyp4f14	cytochrome P450, family 4, subfamily f, polypeptide 14	-2.48	8.4E-04
13516	Epyc	epiphycan	-2.49	2.0E-03
22287	Scgb1a1	secretoglobin, family 1A, member 1 (uteroglobin)	-2.49	1.0E-04
232345	A2m	alpha-2-macroglobulin	-2.49	2.1E-06

SUPPLEMENTARY DATA

GeneID	Symbol	Description	FC	FDR
16780	Lamb3	laminin, beta 3	-2.57	2.1E-05
140904	Caln1	calneuron 1	-2.59	5.4E-04
73712	Dmkn	dermokine	-2.60	1.0E-04
240753	Plekha6	pleckstrin homology domain containing, family A member 6	-2.63	2.6E-05
216166	Plk5	polo-like kinase 5 (Drosophila)	-2.64	1.3E-04
19227	Pthlh	parathyroid hormone-like peptide	-2.66	4.1E-04
53419	Corin	corin	-2.68	1.3E-03
76797	2410137M14Rik	RIKEN cDNA 2410137M14 gene	-2.71	7.4E-03
12386	Ctnna2	catenin (cadherin associated protein), alpha 2	-2.90	4.6E-05
619665	Klf14	Kruppel-like factor 14	-3.11	1.2E-04
64929	Scel	sciellin	-3.66	1.1E-02
76757	Trdn	triadin	-11.43	2.0E-04