

SUPPLEMENTARY DATA

Supplementary Table 1: Gene Expression Levels Measured Using qRT-PCR and Microarrays

Gene Symbol	Entrez Gene ID	P-value qRT-PCR	FC qRT-PCR	P-value Microarrays	FC Microarrays	Correlation
Tph2	216343	1.44E-04	143	4.34E-12	69	0.98
Lipf	67717	1.46E-02	138	1.84E-14	61	0.86
Cpa2	232680	3.63E-02	26	7.82E-12	34	0.83
Ucp1	22227	4.43E-02	28	7.03E-08	33	0.91
Oxtr	18430	2.72E-03	100	5.55E-12	31	0.85

Fold change in expression between the two sample groups (*db/db* and *db/+*) and correlation in expression levels measured by qRT-PCR and microarrays. FC: fold change. P-value microarrays represents Intensity Based Moderated T-statistics (IBMT) p-value of differential expression.

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Supplementary Table 2: Regulated Pathways and Genes

Pathway	Gene Symbol	Entrez Gene ID	Direction of Regulation	P-value	Fold Change
Glycolysis	Fbp2	14120	up	3.60E-03	3.72
	Akr1c13	27384	up	8.71E-05	2.63
	Pfkl	18641	up	5.24E-05	2.02
	Hk3	212032	up	1.02E-02	1.77
	Dlat	235339	up	1.89E-04	1.50
	Galm	319625	up	3.77E-04	1.47
	Aldh3b1	67689	up	9.54E-03	1.42
	Adpgk	72141	up	1.55E-03	1.30
	Tpi1	21991	up	6.48E-05	1.27
	Dld	13382	up	8.94E-03	1.21
	Aldoa	11674	up	4.45E-03	1.13
	Akr1a4	58810	up	7.94E-03	1.10
	Eno2	13807	down	2.57E-04	2.86
	Ldhb	16832	down	6.45E-04	1.98
TCA Cycle	Idh3a	67834	up	8.30E-04	1.49
	Cs	12974	up	4.07E-04	1.19
	Dlst	78920	up	6.93E-03	1.19
	Sucla2	20916	up	3.12E-03	1.17
	Mdh2	17448	up	4.41E-03	1.11
	Mdh1	17449	up	6.50E-03	1.10
Oxidative Phosphorylation	Atp6v0d2	242341	up	2.87E-08	14.07
	Atp6v0a1	11975	up	6.10E-08	2.66

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Pathway	Gene Symbol	Entrez Gene ID	Direction of Regulation	P-value	Fold Change
	Atp6v1c2	68775	up	1.10E-03	1.93
	Atp6v1b2	11966	up	2.16E-04	1.68
	Atp6v1a	11964	up	5.43E-04	1.54
	Cox10	70383	up	2.38E-03	1.45
	Atp6v1h	108664	up	4.44E-03	1.32
	Atp6v0e	11974	up	1.35E-05	1.25
	Atp6v0a2	21871	up	1.18E-02	1.24
	Atp6v1e1	11973	up	1.54E-03	1.22
	Cox6a1	12861	up	1.69E-03	1.18
	Cox5a	12858	up	9.89E-04	1.17
	Ndufb3	66495	up	1.60E-03	1.16
	Ndufb6	230075	up	1.17E-03	1.14
	Cox6b1	110323	up	2.10E-04	1.13
	Atp6v1g2	66237	down	3.45E-03	7.39
	Atp5g1	11951	down	2.49E-03	1.89
	Atp5e	67126	down	1.07E-02	1.09
Fatty Acid Metabolism	Cpt1b	12895	up	2.30E-03	2.59
	Acaa1b	235674	up	1.29E-03	2.50
	Acs11	14081	up	5.41E-06	1.93
	Acox1	11430	up	1.81E-06	1.66
	Slc27a1	26457	up	6.89E-05	1.63
	Acaa1a	113868	up	6.84E-04	1.51
	Hadha	97212	up	4.82E-04	1.51

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Pathway	Gene Symbol	Entrez Gene ID	Direction of Regulation	P-value	Fold Change
	Acaa2	52538	up	2.65E-03	1.43
	Acadm	11364	up	5.20E-05	1.33
	Cpt1a	12894	up	5.20E-03	1.31
	Acadl	11363	up	3.73E-04	1.22
	Cpt1c	78070	down	4.38E-06	1.64
Glycerolipid Metabolism	Lipf	67717	up	1.87E-14	60.63
	Gla	11605	up	1.17E-04	2.56
	Pnpla3	116939	up	3.14E-05	2.42
	Mgll	23945	up	3.09E-06	2.30
	Dgat2	67800	up	1.39E-05	2.01
	Lipe	16890	up	8.11E-04	1.88
	Gpd1	14555	up	1.81E-03	1.64
	Lpl	16956	up	2.84E-06	1.49
	Pnliprp2	18947	up	7.22E-03	1.36
	Dgat1	13350	up	9.94E-03	1.33
	Lycat	225010	up	4.35E-03	1.22
	Agpat7	99010	down	8.85E-03	1.39
Lipid Transport	Apoc4	11425	up	5.75E-10	12.23
	Apoc2	11813	up	2.59E-07	5.14
	Gpihbp1	68453	up	1.62E-05	3.14
	Cpt1b	12895	up	2.30E-03	2.59
	Adfp	11520	up	4.38E-08	2.27
	Atp10a	11982	up	3.44E-04	2.07

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Pathway	Gene Symbol	Entrez Gene ID	Direction of Regulation	P-value	Fold Change
	Vldlr	22359	up	2.16E-07	1.83
	Oprs1	18391	up	4.28E-04	1.77
	Slc27a1	26457	up	6.89E-05	1.63
	Apool	68117	up	1.18E-04	1.58
	Cpt1a	12894	up	5.20E-03	1.31
	Pltp	18830	up	4.10E-04	1.16
	Atp8a2	50769	down	1.62E-03	4.25
	Lcat	16816	down	2.53E-04	2.76
	Osbp13	71720	down	1.13E-02	2.16
	Abca2	11305	down	2.82E-03	1.41
Adipocytokine Signaling	Npy	109648	up	4.21E-03	3.62
	Lep	16846	up	3.83E-06	3.10
	Cpt1b	12895	up	2.30E-03	2.59
	Tnf- α	21926	up	7.42E-03	2.06
	Acs11	14081	up	5.41E-06	1.93
	CD36	12491	up	7.38E-07	1.82
	Ptpn11	19247	up	9.86E-05	1.53
	Tnfrsf1b	21938	up	1.19E-02	1.52
	Mtor	56717	up	1.67E-04	1.44
	Cpt1a	12894	up	5.20E-03	1.31
	Mapk10	26414	down	1.01E-02	15.96
	Lepr	16847	down	5.64E-04	3.02
	Camkk1	55984	down	1.29E-04	2.18

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Pathway	Gene Symbol	Entrez Gene ID	Direction of Regulation	P-value	Fold Change
	Akt3	23797	down	2.06E-04	1.78
	Cpt1c	78070	down	4.38E-06	1.64
PPAR Signaling	Ucp1	22227	up	7.04E-08	33.15
	Olr1	108078	up	3.64E-10	16.93
	Aqp7	11832	up	2.58E-06	2.91
	Cpt1b	12895	up	2.30E-03	2.59
	Acaa1b	235674	up	1.29E-03	2.50
	Angptl4	57875	up	3.86E-05	2.35
	Acs11	14081	up	5.41E-06	1.93
	CD36	12491	up	7.38E-07	1.82
	Acox1	11430	up	1.81E-06	1.66
	Slc27a1	26457	up	6.89E-05	1.63
	Gyk	14933	up	8.21E-03	1.62
	Pparg	19016	up	3.28E-04	1.61
	Acaala	113868	up	6.84E-04	1.51
Cpt1c	78070	down	4.38E-06	1.64	
Neurotrophin Signaling	Irak2	108960	up	2.65E-10	4.61
	Pik3r5	320207	up	1.39E-04	3.05
	Sort1	20661	up	1.43E-04	1.65
	Ripk2	192656	up	4.43E-05	1.56
	Mapk10	26414	down	1.01E-02	15.96
	Ngfr	18053	down	1.08E-03	2.57
	Ntrk3	18213	down	4.26E-03	2.10

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Pathway	Gene Symbol	Entrez Gene ID	Direction of Regulation	P-value	Fold Change
	Ngfb	18049	down	6.04E-03	1.53
Axonogenesis	Tnfrsf12a	27279	up	6.44E-05	3.03
	Alcam	11658	up	1.82E-05	2.28
	Cxcr4	12767	up	1.70E-03	1.75
	Ptpn11	19247	up	9.86E-05	1.53
	Nefm	18040	down	1.32E-03	23.62
	Nefl	18039	down	1.91E-03	19.43
	Pou4f2	18997	down	8.78E-03	8.79
	Sema4f	20355	down	3.89E-03	8.47
	Ptprz1	19283	down	7.97E-03	6.72
	Gap43	14432	down	3.77E-03	4.70
	Kif5c	16574	down	1.35E-03	4.43
	L1cam	16728	down	2.52E-03	3.77
	Slitrk5	75409	down	1.91E-03	3.48
	Thy1	21838	down	1.68E-06	3.25
	Rab3a	19339	down	4.20E-03	3.12
	Mapt	17762	down	1.01E-03	2.74
	Stxbp1	20910	down	1.95E-03	2.71
	Ngfr	18053	down	1.08E-03	2.57
	Myh10	77579	down	5.76E-07	2.44
	Bmp7	12162	down	1.01E-04	2.33
Gfra3	14587	down	4.87E-03	2.13	
Ntrk3	18213	down	4.26E-03	2.10	

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Pathway	Gene Symbol	Entrez Gene ID	Direction of Regulation	P-value	Fold Change
	S100b	20203	down	1.34E-04	2.09
	Plxnb1	235611	down	1.66E-03	1.99
	Foxd1	15229	down	1.39E-03	1.95
	Etv1	14009	down	2.52E-03	1.81
	Tgfb2	21808	down	3.03E-04	1.71
	Amigo1	229715	down	9.10E-04	1.68
	Limk1	16885	down	3.47E-03	1.61
	Fyn	14360	down	1.09E-06	1.61
	Ntng1	80883	down	6.01E-04	1.59
	Cdh4	12561	down	6.01E-04	1.59
	Ngfb	18049	down	6.51E-03	1.56
	Kif2a	16563	down	6.04E-03	1.53
Apoptosis	Brca1	12189	up	1.90E-05	3.63
	Hipk2	15258	up	7.26E-07	3.41
	Igfbp3	16009	up	6.88E-07	3.21
	Cd1d1	12479	up	2.00E-08	2.91
	Hipk1	15257	up	1.68E-04	2.37
	Tnfrsf10b	21933	up	3.58E-05	2.21
	Il1a	16175	up	9.01E-03	2.14
	Tnf- α	21926	up	7.42E-03	2.06
	Ripk3	56532	up	8.76E-03	2.05
	Aifm2	71361	up	4.46E-04	2.04
	BCI2113	94044	up	3.95E-06	1.97

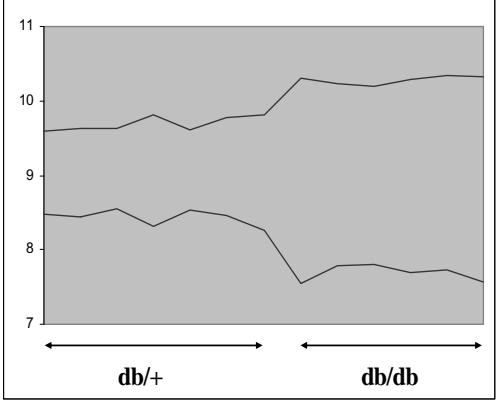
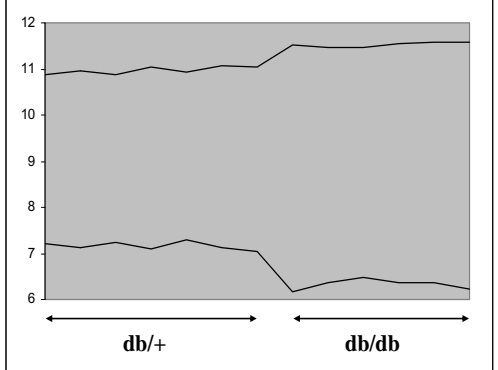
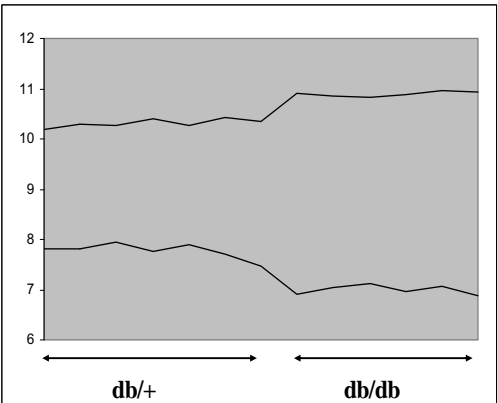
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Pathway	Gene Symbol	Entrez Gene ID	Direction of Regulation	P-value	Fold Change
	Casp8	12370	up	1.93E-03	1.91
	Bcl2l10	12049	up	1.01E-03	1.88
	Psen2	19165	up	4.07E-05	1.62
	Ripk2	192656	up	4.43E-05	1.56
	Cebpb	12608	up	1.78E-03	1.55
	Fas	14102	up	8.80E-03	1.39
	Agtr1b	11608	down	7.11E-06	4.38
	Mapk8ip1	19099	down	3.16E-04	2.51
	Tgfb2	21808	down	3.03E-04	1.71

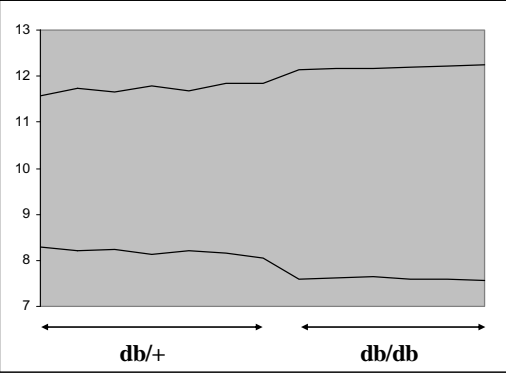
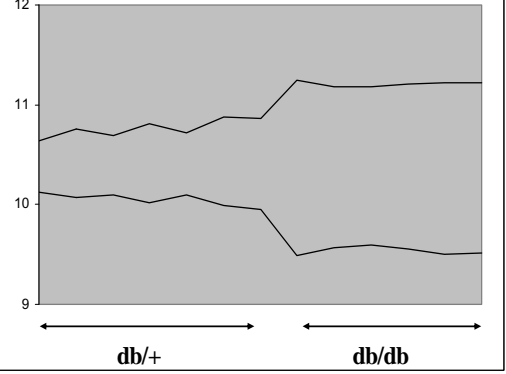
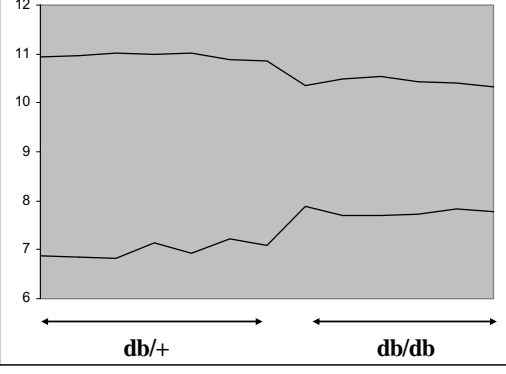
Pathways and associated genes up- or down-regulated in the *db/db* samples. P-value represents Intensity Based Moderated T-statistics (IBMT) p value of differential expression.

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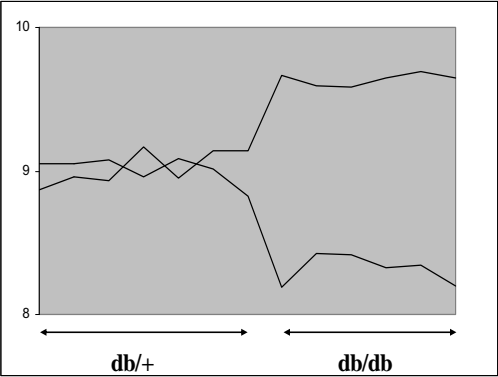
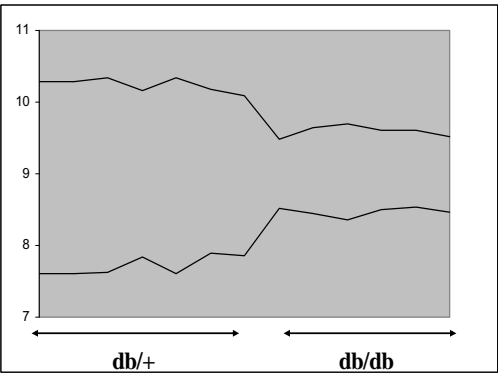
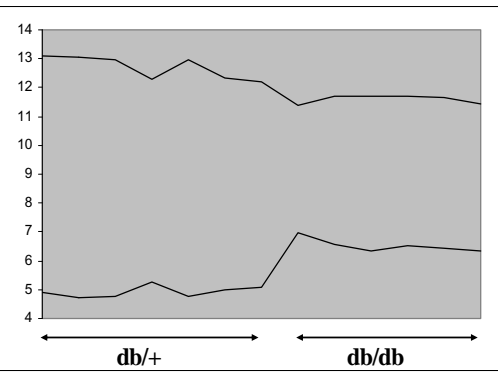
Supplementary Table 3: Expression Profile Clusters and Enrichment

Expression Profile	Number of Genes	Enriched Terms
	321	Endoplasmic reticulum Cytoplasm Regulation of axonogenesis Golgi apparatus Regulation of actin cytoskeleton Protein transport
	283	Cytoplasm Mitochondrion Protein transport Endoplasmic reticulum Lipid transport Lipid metabolic process
	275	Cytoplasm Lipid metabolic process Mitochondrion Endoplasmic reticulum Protein transport Nervous system development Carbohydrate metabolic process

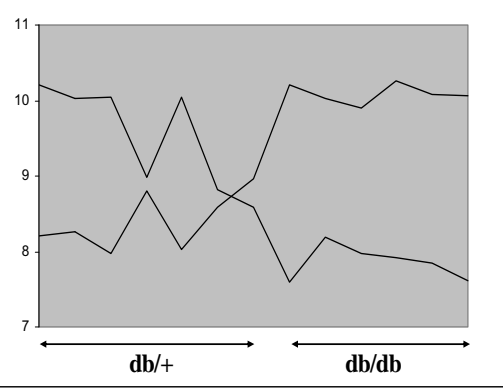
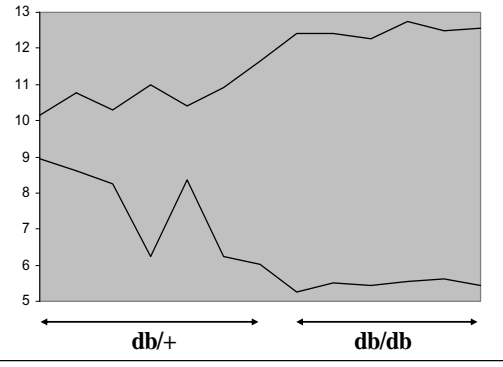
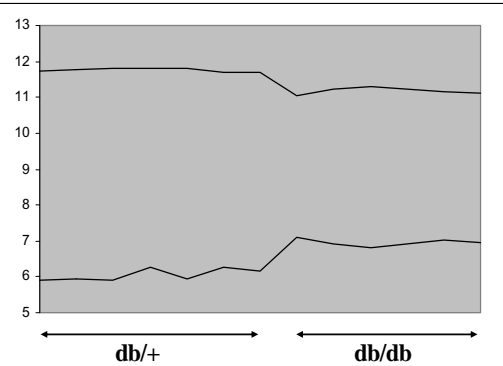
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Expression Profile	Number of Genes	Enriched Terms
	253	<p>Cytoplasm</p> <p>Mitochondrion</p> <p>Golgi apparatus</p> <p>Oxidoreductase activity</p> <p>Endoplasmic reticulum</p> <p>Vesicle mediated transport</p> <p>Lipid metabolic process</p>
	260	<p>Mitochondrion</p> <p>Cytoplasm</p> <p>Extracellular matrix</p> <p>Oxidoreductase activity</p> <p>Antioxidant activity</p>
	263	<p>Regulation of transcription</p> <p>Metal ion binding</p> <p>Cell cycle</p> <p>Anatomical structure development</p> <p>RNA splicing</p> <p>Fat cell differentiation</p>

SUPPLEMENTARY DATA

Expression Profile	Number of Genes	Enriched Terms
	260	<p>Cytoplasm</p> <p>RIG-I-like receptor signaling pathway</p> <p>Endoplasmic reticulum</p> <p>Vitamin transport</p> <p>Protein transport</p>
	279	<p>Cytoskeleton</p> <p>Cell division</p> <p>Negative regulation of transport</p> <p>Regulation of RAS protein signal transduction</p> <p>Neuromuscular junction development</p> <p>Response to DNA damage stimulus</p> <p>Focal adhesion</p>
	110	<p>Cell division</p> <p>Mitotic cell cycle</p> <p>Microtubule cytoskeleton</p> <p>Response to stress</p> <p>Response to DNA damage</p> <p>Neuron projection development</p>

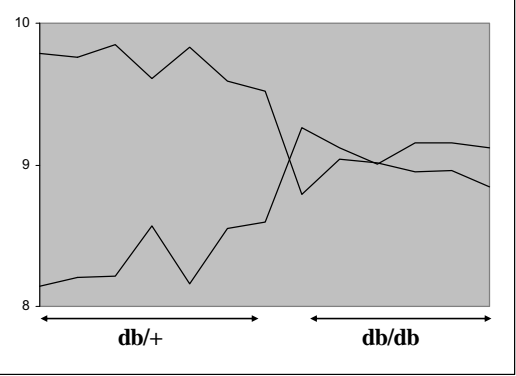
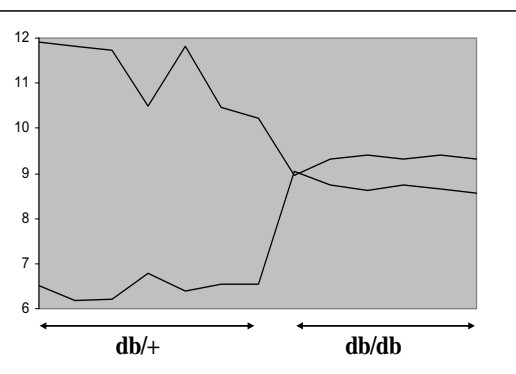
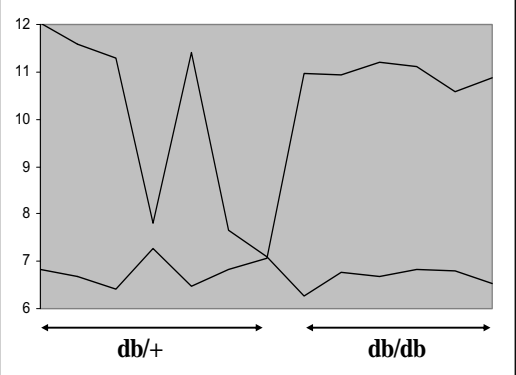
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Expression Profile	Number of Genes	Enriched Terms
	109	<p>Cell junction</p> <p>Cell adhesion molecules (CAMs)</p> <p>Cell adhesion</p> <p>Synapse</p> <p>Neuron projection</p>
	149	<p>Metal ion transport</p> <p>Synaptic vesicle</p> <p>Voltage-gated ion channel activity</p> <p>Neurotransmitter transport</p> <p>Neuron projection development</p> <p>Cell-cell signaling</p>
	216	<p>Dendrite</p> <p>Nucleus</p> <p>Cell-matrix adhesion</p> <p>Neuron projection</p> <p>Extracellular matrix</p> <p>Cellular response to stress</p> <p>Regulation of cell communication</p>

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Expression Profile	Number of Genes	Enriched Terms
	102	<p>Ion transmembrane transporter activity</p> <p>Neuroactive ligand-receptor interaction</p> <p>Cell-cell signaling</p> <p>Transmission of nerve impulse</p> <p>Cell communication</p> <p>Neurotransmitter receptor activity</p>
	150	<p>Extracellular region</p> <p>Carbohydrate catabolic process</p> <p>Positive regulation of cell cycle</p> <p>ATP synthesis coupled proton transport</p> <p>Alzheimer's disease</p> <p>Oxidative phosphorylation</p> <p>Glycolysis</p>
	127	<p>Plasma membrane</p> <p>Exocytosis</p> <p>Cell junction</p> <p>Synapse</p> <p>Neuroactive ligand-receptor interaction</p> <p>Axon</p>

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Expression Profile	Number of Genes	Enriched Terms
	247	<ul style="list-style-type: none"> Regulation of cell cycle process Leukocyte chemotaxis Cytoplasm Cell adhesion Regulation of response to stress Glycan biosynthesis Positive regulation of NF-κB
	117	<ul style="list-style-type: none"> Cell division Response to wounding Chemokine activity Inflammatory response Extracellular region Microtubule cytoskeleton Chemokine signaling pathway
	51	<ul style="list-style-type: none"> Neuron projection Neurofilament cytoskeleton Axon Amyotrophic lateral sclerosis (ALS) Extracellular region Vesicle mediated transport

CRC expression profile clusters and enrichment. X axis: seven *db/+* and six *db/db* samples, y axis: \log_2 expression level. Shown are mean expression levels for up-regulated and down-regulated genes in each cluster. Enriched terms with P value < 0.05 are listed for each cluster.

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Supplementary Table 4: Over-represented TFBS Matrix Families and Regulated TFs

TFBS Family	TF Gene Symbol	Entrez Gene ID	Direction of Regulation	P-value	Fold Change
HOMF	Msx1	17701	down	9.05E-03	1.70
ETSF	Etv3	27049	up	6.13E-03	1.24
	Etv1	14009	down	4.52E-03	1.81
	Fli1	14247	up	1.72E-02	1.41
	Sfpi1	20375	up	1.99E-02	1.74
HOXF	Hoxd1	15429	down	2.47E-02	20.12
	Hoxb5	15413	down	1.00E-02	5.88
	Hoxb6	15414	down	4.20E-03	5.48
	Hoxb2	103889	down	9.31E-04	2.19
	Hoxb4	15412	down	1.11E-03	1.66
	Hoxa5	15402	down	4.53E-03	1.51
HBOX	Meox1	17285	down	2.84E-03	1.42
LHXF	Isl1	16392	down	4.57E-03	33.44
	Isl2	104360	down	2.05E-02	19.55
OCT1	-	-	-	-	-

TFBS matrix families and TFs belonging to the matrix families, up- or down-regulated in the *db/db* samples. No TF from OCT1 family was differentially regulated in our data. P-value represents IBMT p value of differential expression.