

A key role for neuropeptide Y in lifespan extension and cancer suppression via dietary restriction

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Supplemental figures S1-S5 and supplemental table S1-S11

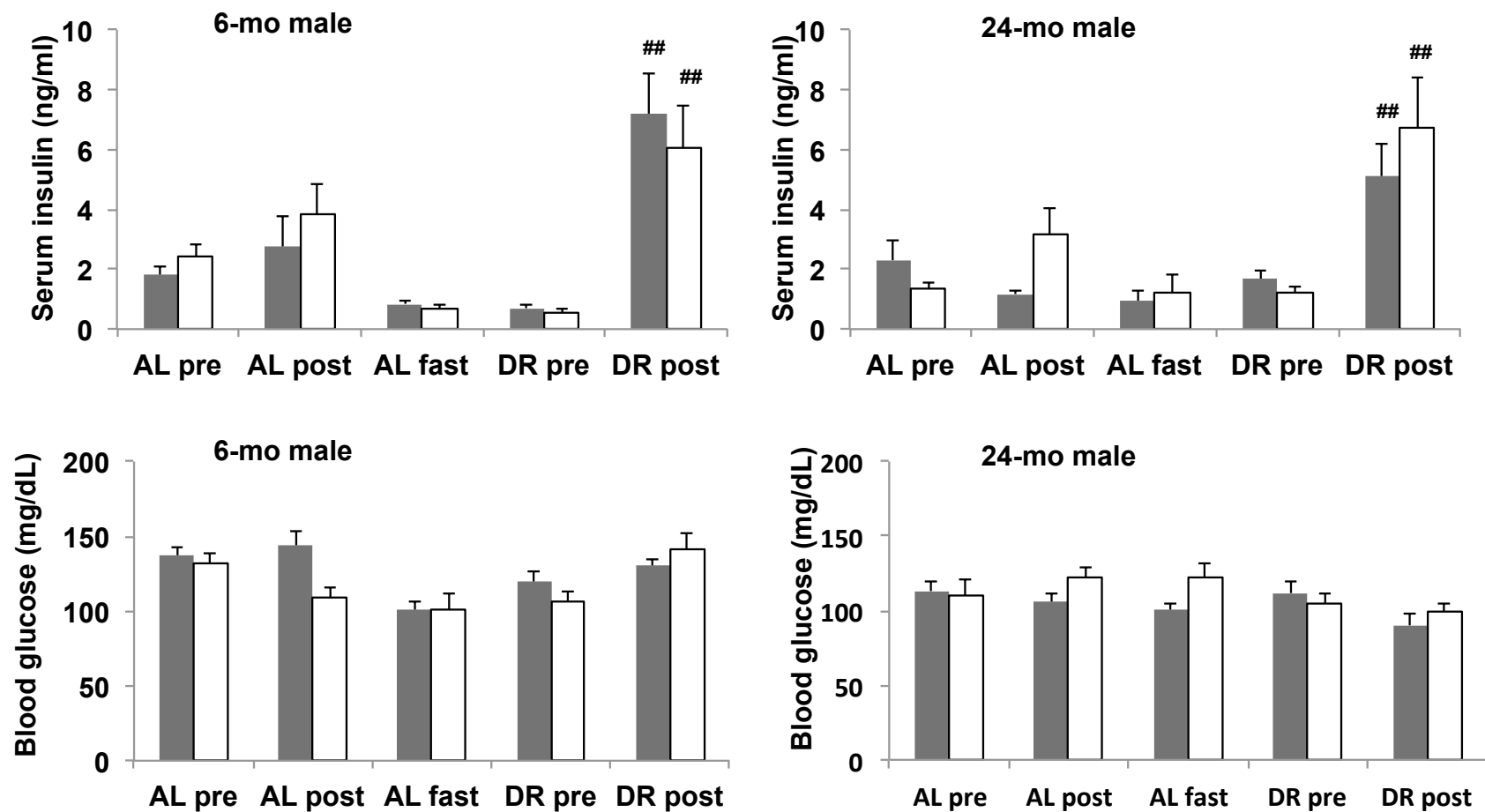


Fig. S1. Plasma insulin and blood glucose concentrations at 6 and 24 months of age. The values represent means $\pm$ SE ($n = 4$ to 7). Dark gray bars represent the WT mice; white bars represent the $Npy^{-/-}$ mice. “pre” and “post” represent preprandial and postprandial phases of a feeding cycle respectively. The AL groups were also subjected to overnight fasting to compare the insulin and glucose levels with

those in the DR pre groups. ##, $p < 0.01$ vs the respective the DR pre groups.

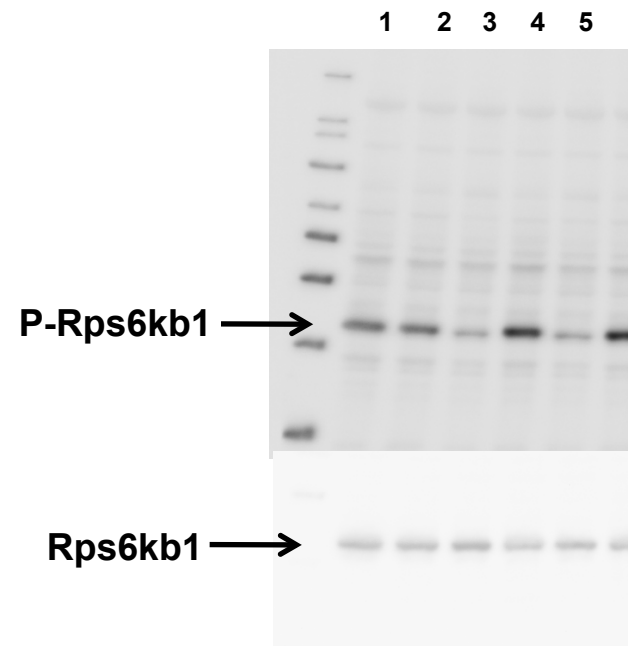


Fig. S2. Western blots of phosphorylated (an active form) and total ribosomal protein S6 kinase polypeptide 1 (Rps6kb1). Representative western blots. Lane 1, positive control; lane 2, WT-AL; lane 3, WT-DR; lane 4, Npy^{-/-}-AL; lane 5, Npy^{-/-}-DR.

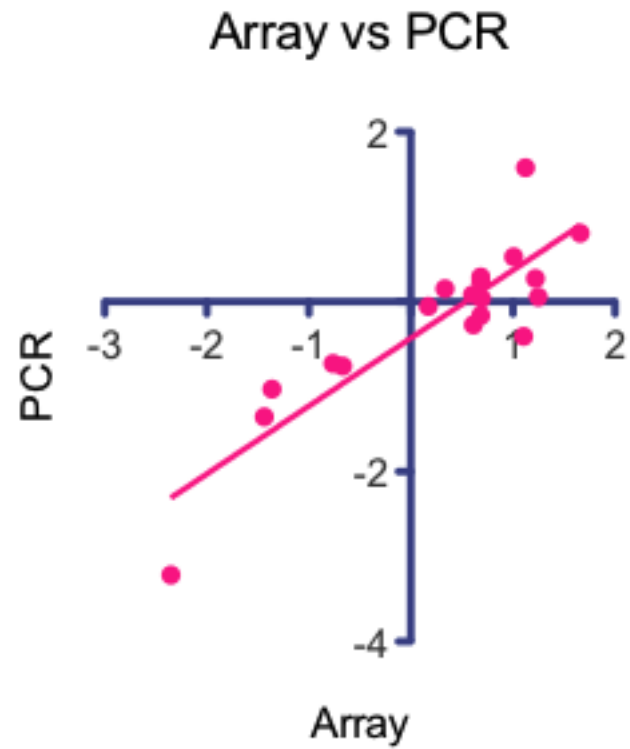


Fig. S3. A scatter plot between the fold changes ($Npy^{-/-}$ -DR/ WT-DR) calculated by the microarray data and qRT-PCR data. A linear regression model; $R^2 = 0.7717$; $p < 0.0001$.

Table S1. The mRNA expression levels of uncoupling protein (Ucp) 1, 2, and 3 in the brown adipose tissue in the 6-month-old male mice.

	WT-AL	WT-DR	Npy ^{-/-} -AL	Npy ^{-/-} -DR
Actb	1.00 (0.08)	1.05 (0.04)	0.92 (0.05)	1.23 (0.12)
Ucp1/Actb	1.00 (0.10)	0.94 (0.08)	0.77 (0.13)	1.01 (0.14)
Ucp2/Actb	1.00 (0.07)	1.10 (0.13)	1.15 (0.10)	1.15 (0.06)
Ucp3/Actb	1.00 (0.12)	0.93 (0.06)	0.82 (0.13)	1.04 (0.10)

Values represent the means (SE, n = 4 ~ 6) of mRNA expression levels normalized by the level in the WT-AL. Actb, b-actin.

Table S2. The weights of white adipose and brown adipose tissues in 6-month-old male mice

	WT-AL	WT-DR	Npy ^{-/-} -AL	Npy ^{-/-} -DR
WAT (mg)	1612 (324)	908 (84) [#]	2481 (171)**	474 (104) ^{###}
WAT (mg/g BW)	48.5 (7.0)	34.3 (2.4) [#]	61.9 (2.3)*	20.1 (3.7) ^{###/&}
BAT (mg)	116 (13)	99 (7)	183 (25)**	63 (9) ^{###}
BAT (mg/g BW)	3.6 (0.4)	3.8 (0.3)	4.5 (0.4)	2.7 (0.2) ^{##}

Values represent the means (S.E., n = 4~6). WAT, white adipose tissue; the sum of weights of peri-renal and epididymal white adipose tissues. BAT, brown adipose tissue. *, p < 0.05 and **, p < 0.01 versus (vs) WT-AL. #, p < 0.05, ##, p < 0.01, ###, p < 0.001 vs respective AL groups. &, p < 0.05 vs WT-DR

Table S3. List of pathways enriched in genes upregulated in the WT-DR compared to the WT-AL mouse liver: Gene set enrichment analysis (GSEA) using Molecular Signatures Database (MsigDB).

Pathway Name	P-value	Q-value	Gene	Pathway Description
GNF2_TST	0.0000	0.0036	APCS HSD17B6 ALDH1L1 CES1 ORM2 SLC22A7 DCXR	http://www.broadinstitute.org/gsea/msigdb/cards/GNF2_TST.html
GNF2_GSTM1	0.0000	0.0036	APCS HSD17B6 ALDH1L1 CES1 ORM2 SLC22A7 DCXR	http://www.broadinstitute.org/gsea/msigdb/cards/GNF2_GSTM1.html
CHIANG_LIVER_CANCER_SUBCLASS PROLIFERATION_DN	0.0000	0.0036	MYO1B ALDH1L1 DCXR SULT1B1 SLC2A2 GPT HSD17B6 FMO3	http://www.broadinstitute.org/gsea/msigdb/cards/CHIANG_LIVER_CANCER_SUBCLASS_PROLIFERATION_DN.html
WOO_LIVER_CANCER_RECURRENCE DN	0.0000	0.0036	CPS1 SLC2A2 GPT ALDH1L1 DCXR SULT1B1	http://www.broadinstitute.org/gsea/msigdb/cards/WOO_LIVER_CANCER_RECURRENCE_DN.html
GNF2_CYP2B6	0.0000	0.0036	APCS DCXR HSD17B6 CES1 ORM2	http://www.broadinstitute.org/gsea/msigdb/cards/GNF2_CYP2B6.html
GNF2_LCAT	0.0000	0.0036	APCS HSD17B6 ALDH1L1 CES1 ORM2 SLC22A7 DCXR	http://www.broadinstitute.org/gsea/msigdb/cards/GNF2_LCAT.html
LEE_LIVER_CANCER_MYC_E2F1_UP	0.0000	0.0038	FMO3 RAD51L1 LPL CYP39A1 PTGDS	http://www.broadinstitute.org/gsea/msigdb/cards/LEE_LIVER_CANCER_MYC_E2F1_UP.html
GNF2_HPND	0.0000	0.0038	ALDH1L1 DCXR APCS HSD17B6 CES1 ORM2 SLC22A7	http://www.broadinstitute.org/gsea/msigdb/cards/GNF2_HPND.html

GNF2_HPX	0.0000	0.0038	ALDH1L1 DCXR APCS HSD17B6 CES1 ORM2 SLC22A7	http://www.broadinstitute.org/gsea/msigdb/cards/GNF2_HPX.html
WU_CELL_MIGRATION	0.0000	0.0038	ARHGAP29 WWTR1 TNFAIP2 SQRDL GJA1 BST2 GSTM3 HMGA2	http://www.broadinstitute.org/gsea/msigdb/cards/WU_CELL_MIGRATION.html
GNF2_CEBPA	0.0001	0.0064	APCS HSD17B6 CES1 ORM2 DCXR	http://www.broadinstitute.org/gsea/msigdb/cards/GNF2_CEBPA.html
HOSHIDA_LIVER_CANCER_SUBCLASS_S3	0.0001	0.0076	CPS1 SLC2A2 ALDH1B1 PTGR1 SREBF1 ASCL1 APCS GPT CES1	http://www.broadinstitute.org/gsea/msigdb/cards/HOSHIDA_LIVER_CANCER_SUBCLASS_S3.html
CAIRO_LIVER_DEVELOPMENT_DN	0.0002	0.0104	PLA1A ALDH1L1 DCXR SQRDL STAB2 CPS1 ALDH1B1 RDH5	http://www.broadinstitute.org/gsea/msigdb/cards/CAIRO_LIVER_DEVELOPMENT_DN.html
NAKAYAMA_SOFT_TISSUE_TUMORS_PCA2_DN	0.0003	0.0145	NTRK2 CES1 PLA2G16 LPL BST2	http://www.broadinstitute.org/gsea/msigdb/cards/NAKAYAMA_SOFT_TISSUE_TUMORS_PCA2_DN.html

LEE_LIVER_CANCER_SURVIVAL_UP	0.0003	0.0177	DCXR SLC2A2 APCS CES1 FMO3 RDH5	http://www.broadinstitute.org/gsea/msigdb/cards/LEE_LIVER_CANCER_SURVIVAL_UP.html
WILLERT_WNT_SIGNALING	0.0004	0.0177	GSTM3 GYPC GJA1	http://www.broadinstitute.org/gsea/msigdb/cards/WILLERT_WNT_SIGNALING.html
SU_LIVER	0.0007	0.0305	FMO3 CPS1 APCS GPT	http://www.broadinstitute.org/gsea/msigdb/cards/SU_LIVER.html
GNF2_IGF1	0.0008	0.0341	HSD17B6 APCS ORM2	http://www.broadinstitute.org/gsea/msigdb/cards/GNF2_IGF1.html
LEE_LIVER_CANCER_E2F1_UP	0.0009	0.0341	FMO3 RAD51L1 LPL CYP39A1	http://www.broadinstitute.org/gsea/msigdb/cards/LEE_LIVER_CANCER_E2F1_UP.html
REACTOME_REGULATION_OF_LIPID_METABOLISM_BY_PEROXISOME_PROLIFERATOR_ACTIVATED_RECEPTOR_ALPHA	0.0009	0.0341	SLC2A2 SREBF1 LPL FASN	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME_REGULATION_OF_LIPID_METABOLISM_BY_PEROXISOME_PROLIFERATOR_ACTIVATED_RECEPTOR_ALPHA.html

CHIARADONNA NEOPLASTIC TRANSFORMATION KRAS CDC25 UP	0.0009	0.0341	WWTR1 HMGA2 VAMP5 GJA1	http://www.broadinstitute.org/gsea/msigdb/cards/CHIARADONNA NEOPLASTIC TRANSFORMATION_KRAS_CDC25_UP.html
HORMONE METABOLIC PROCESS	0.0015	0.0502	HSD17B6 BMP6 SULT1B1	http://www.broadinstitute.org/gsea/msigdb/cards/HORMONE_METABOLIC_PROCESS.html
CARBOXYLESTERASE ACTIVITY	0.0015	0.0502	LPL PLA1A CES1	http://www.broadinstitute.org/gsea/msigdb/cards/CARBOXYLESTERASE_ACTIVITY.html
HSIAO LIVER SPECIFIC GENES	0.0016	0.0503	CPS1 SLC2A2 FMO3 PTGR1 APCS GPT CES1	http://www.broadinstitute.org/gsea/msigdb/cards/HSIAO_LIVER_SPECIFIC_GENES.html
CAR_HPX	0.0018	0.0550	CPS1 APCS HSD17B6 FMO3	http://www.broadinstitute.org/gsea/msigdb/cards/CAR_HPX.html
LIPID METABOLIC PROCESS	0.0019	0.0550	BMP6 CYP39A1 PLA1A LPL PTGDS MGST3 SREBF1 HSD17B6	http://www.broadinstitute.org/gsea/msigdb/cards/LIPID_METABOLIC_PROCESS.html

YAMASHITA_LIVER_CANCER_STEM_CELL_DN	0.0020	0.0550	APCS ALDH1L1 CES1 FMO3	http://www.broadinstitute.org/gsea/msigdb/cards/YAMASHITA_LIVER_CANCER_STEM_CELL_DN.html
REACTOME_BIOLOGICAL_OXIDATIONS	0.0022	0.0550	MGST3 CYP26A1 CYP39A1 FMO3 SULT1B1	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME_BIOLOGICAL_OXIDATIONS.html
OSAWA_TNF_TARGETS	0.0022	0.0550	TNFAIP2 COL3A1	http://www.broadinstitute.org/gsea/msigdb/cards/OSAWA_TNF_TARGETS.html
GARGALOVIC_RESPONSE_TO_OXIDIZED_PHOSPHOLIPIDS_LIGHTYELLOW_DN	0.0022	0.0550	RARB CIRBP	http://www.broadinstitute.org/gsea/msigdb/cards/GARGALOVIC_RESPONSE_TO_OXIDIZED_PHOSPHOLIPIDS_LIGHTYELLOW_DN.html
CHIARADONNA_NEOPLASTIC_TRANSFORMATION_KRAS_UP	0.0022	0.0550	GREM2 MYO1B TNFAIP2 GJA1 HMGA2	http://www.broadinstitute.org/gsea/msigdb/cards/CHIARADONNA_NEOPLASTIC_TRANSFORMATION_KRAS_UP.html
ACUTE_INFLAMMATORY_RESPONSE	0.0027	0.0637	APCS ORM2	http://www.broadinstitute.org/gsea/msigdb/cards/ACUTE_INFLAMMATORY_RESPONSE.html

CAIRO_HEPATOBLASTOMA_DN	0.0030	0.0685	GREM2 CYP26A1 CYP39A1 PLA2G16 SLC22A7 STAB2 HSD17B6	http://www.broadinstitute.org/gsea/msigdb/cards/CAIRO_HEPATOBLASTOMA_DN.html
MICROSOME	0.0031	0.0697	FMO3 MGST3 CYP39A1	http://www.broadinstitute.org/gsea/msigdb/cards/MICROSOME.html
PICCALUGA_ANGIOIMMUNOBLASTIC_LYMPHOMA_UP	0.0033	0.0698	COL3A1 ARHGAP29 WWTR1 GJA1 PTGDS COX7A1	http://www.broadinstitute.org/gsea/msigdb/cards/PICCALUGA_ANGIOIMMUNOBLASTIC_LYMPHOMA_UP.html
VARELA_ZMPSTE24_TARGETS_UP	0.0033	0.0698	CYP26A1 CIRBP CYP2C39	http://www.broadinstitute.org/gsea/msigdb/cards/VARELA_ZMPSTE24_TARGETS_UP.html
RICKMAN_HEAD_AND_NECK_CANCER_E	0.0035	0.0698	NTRK2 CYP26A1 CES1 FMO3	http://www.broadinstitute.org/gsea/msigdb/cards/RICKMAN_HEAD_AND_NECK_CANCER_E.html
VESICULAR_FRACTION	0.0036	0.0698	FMO3 MGST3 CYP39A1	http://www.broadinstitute.org/gsea/msigdb/cards/VESICULAR_FRACTION.html

LEE_TARGETS_OF_PTCH1_AND_SUF U_UP	0.0036	0.0698	ALDH1L1 CNP GJA1 PTGDS	http://www.broadinstitute.org/gsea/msigdb/cards/LEE_TARGETS_OF_PTCH1_AND_SUFU_UP.html
CHANDRAN_METASTASIS_TOP50_DN	0.0037	0.0698	ETHE1 CIRBP	http://www.broadinstitute.org/gsea/msigdb/cards/CHANDRAN_METASTASIS_TOP50_DN.html
NIKOLSKY_BREAST_CANCER_1Q32_AMP LICON	0.0037	0.0698	FCAMR IKBKE	<a href="http://www.broadinstitute.org/gsea/msigdb/cards/NIKOLSKY_BREAST_CANCER_1Q32_AMP
LICON.html">http://www.broadinstitute.org/gsea/msigdb/cards/NIKOLSKY_BREAST_CANCER_1Q32_AMP LICON.html
ONKEN_UVEAL_MELANOMA_DN	0.0042	0.0739	ALDH1L1 GYPC ETHE1 RPL3 RARB GSTM3 PDE4B PLA1A CPS1 CIRBP	http://www.broadinstitute.org/gsea/msigdb/cards/ONKEN_UVEAL_MELANOMA_DN.html
SWEET_LUNG_CANCER_KRAS_DN	0.0043	0.0739	GREM2 BMP6 COL3A1 MYO1B WWTR1 FMO3 MFAP5 INMT COX7A1	http://www.broadinstitute.org/gsea/msigdb/cards/SWEET_LUNG_CANCER_KRAS_DN.html
CYCLIC_NUCLEOTIDE_PHOSPHODI ESTERASE_ACTIVITY	0.0043	0.0739	PDE4B CNP	<a href="http://www.broadinstitute.org/gsea/msigdb/cards/CYCLIC_NUCLEOTIDE_PHOSPHODI
ESTERASE_ACTIVITY.html">http://www.broadinstitute.org/gsea/msigdb/cards/CYCLIC_NUCLEOTIDE_PHOSPHODI ESTERASE_ACTIVITY.html

YAMASHITA_LIVER_CANCER_WITH_EPCAM_DN	0.0043	0.0739	ALDH1L1 CES1	http://www.broadinstitute.org/gsea/msigdb/cards/YAMASHITA_LIVER_CANCER_WITH_EPCAM_DN.html
GLUTATHIONE_TRANSFERASE_ACTIVITY	0.0050	0.0812	MGST3 GSTM3	http://www.broadinstitute.org/gsea/msigdb/cards/GLUTATHIONE_TRANSFERASE_ACTIVITY.html
CHANG_IMMORTALIZED_BY_HP31_UP	0.0050	0.0812	SLC2A2 LTBP1	http://www.broadinstitute.org/gsea/msigdb/cards/CHANG_IMMORTALIZED_BY_HP31_UP.html
YAO_TEMPORAL_RESPONSE_TO_PROGESTERONE_CLUSTER_8	0.0051	0.0819	CYP26A1 CAPRIN2 PNKD	http://www.broadinstitute.org/gsea/msigdb/cards/YAO_TEMPORAL_RESPONSE_TO_PROGESTERONE_CLUSTER_8.html
PETRETTO_HEART_MASS_QTL_CIS_DN	0.0057	0.0878	GJA1 SQRDL	http://www.broadinstitute.org/gsea/msigdb/cards/PETRETTO_HEART_MASS_QTL_CIS_DN.html
LEE_LIVER_CANCER_MYC_UP	0.0057	0.0878	MGST3 CYP26A1 LPL	http://www.broadinstitute.org/gsea/msigdb/cards/LEE_LIVER_CANCER_MYC_UP.html

REACTOME_METABOLISM_OF_LIPIDS_AND_LIPOPROTEINS	0.0059	0.0878	SREBF1 CYP39A1 LPL FASN PPM1L SLC2A2	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME_METABOLISM_OF_LIPIDS_AND_LIPOPROTEINS.html
LE_EGR2_TARGETS_DN	0.0075	0.1097	MGST3 MYO1B LPL PTGDS	http://www.broadinstitute.org/gsea/msigdb/cards/LE_EGR2_TARGETS_DN.html
LEE_LIVER_CANCER_CIPROFIBRATE_UP	0.0082	0.1125	APCS RAD51L1 LPL	http://www.broadinstitute.org/gsea/msigdb/cards/LEE_LIVER_CANCER_CIPROFIBRATE_UP.html
BROWNE_HCMV_INFECTION_18HR_DN	0.0084	0.1125	CACNA1A COL3A1 VAMP5 CIRBP RDH5	http://www.broadinstitute.org/gsea/msigdb/cards/BROWNE_HCMV_INFECTION_18HR_DN.html
LEE_LIVER_CANCER_MYC_TGFA_UP	0.0086	0.1125	RAD51L1 LPL CYP39A1	http://www.broadinstitute.org/gsea/msigdb/cards/LEE_LIVER_CANCER_MYC_TGFA_UP.html
LEE_LIVER_CANCER_DENA_UP	0.0086	0.1125	APCS RAD51L1 LPL	http://www.broadinstitute.org/gsea/msigdb/cards/LEE_LIVER_CANCER_DENA_UP.html

LEE_LIVER_CANCER_ACOX1_UP	0.0086	0.1125	APCS RAD51L1 LPL	http://www.broadinstitute.org/gsea/msigdb/cards/LEE_LIVER_CANCER_ACOX1_UP.html
CELLULAR_LIPID_METABOLIC_PROCESS	0.0087	0.1125	BMP6 CYP39A1 PLA1A LPL PTGDS HSD17B6	http://www.broadinstitute.org/gsea/msigdb/cards/CELLULAR_LIPID_METABOLIC_PROCESS.html
FARMER_BREAST_CANCER_CLUSTER_7	0.0088	0.1125	SREBF1 FASN	http://www.broadinstitute.org/gsea/msigdb/cards/FARMER_BREAST_CANCER_CLUSTER_7.html
LIANG_SILENCED_BY_METHYLATION_UP	0.0088	0.1125	COX7A1 MFAP5	http://www.broadinstitute.org/gsea/msigdb/cards/LIANG_SILENCED_BY_METHYLATION_UP.html

The pathways delineated by genes down-regulated in the Npy^{-/-}-DR compared to the WT-DR are noted by red letters.

Table S4. List of pathways enriched in genes down-regulated in the WT-DR compared to the WT-AL mouse liver.

Pathway Name	P-value	Q-value	Gene	Pathway Description
ICHIBA_GRAFT_VERSUS_HOST_DISEASE_35D_DN	0.0000	0.0572	CYP8B1 CYP7B1 MUP4 ACSL1 RETSAT VNN1 MUP3	http://www.broadinstitute.org/gsea/msigdb/cards/ICHIBA_GRAFT_VERSUS_HOST_DISEASE_35D_DN.html
LEE_LIVER_CANCER_DENA_DN	0.0001	0.0758	PEX11A EHHADH CYP7B1 EPHX2 CSAD ACSL1 ME1	http://www.broadinstitute.org/gsea/msigdb/cards/LEE_LIVER_CANCER_DENA_DN.html
REACTOME_METABOLISM_OF_LIPIDS_AND_LIPOPROTEINS	0.0001	0.0769	TM7SF2 CYP8B1 HSD17B7 CRAT ACSL1 ME1 ACOT8 PEX11A ABCB4 EHHADH CYP7B1 NSDHL	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME_METABOLISM_OF_LIPIDS_AND_LIPOPROTEINS.html
OXIDOREDUCTASE_ACTIVITY_GO_0016616	0.0002	0.0798	LDHA NSDHL UGDH EHHADH ME1 HSD17B7	http://www.broadinstitute.org/gsea/msigdb/cards/OXIDOREDUCTASE_ACTIVITY_GO_0016616.html
LEE_LIVER_CANCER_MYC_E2F1_DN	0.0002	0.0798	EPHX2 ACSL1 CYP7B1 ME1 RARRES1 ELOVL5	http://www.broadinstitute.org/gsea/msigdb/cards/LEE_LIVER_CANCER_MYC_E2F1_DN.html
REACTOME_STEROID_METABOLISM	0.0003	0.0798	ACOT8 TM7SF2 NSDHL CYP8B1 CYP7B1 HSD17B7	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME_STEROID_METABOLISM.html
OXIDOREDUCTASE_ACTIVITY_ACTING_ON_CH_OH_GROUP_OF_DONORS	0.0003	0.0798	LDHA UGDH EHHADH HSD17B7 NSDHL ME1	http://www.broadinstitute.org/gsea/msigdb/cards/OXIDOREDUCTASE_ACTIVITY_ACTING_ON_CH_OH_GROUP_OF_DONORS.html
REACTOME_TRANSFORMATION_OF_F_LANOSTEROL_TO_CHOLESTEROL	0.0003	0.0798	HSD17B7 TM7SF2 NSDHL	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME_TRANSFORMATION_OF_F_LANOSTEROL_TO_CHOLESTEROL.html
KEGG_PEROXISOME	0.0009	0.1855	ACOT8 PEX11A EHHADH CRAT EPHX2 ACSL1	http://www.broadinstitute.org/gsea/msigdb/cards/KEGG_PEROXISOME.html
LE_EGR2_TARGETS_DN	0.0010	0.1855	TMEM56 FDPS CLTB GNAI1 NSDHL CYP51 ME1	http://www.broadinstitute.org/gsea/msigdb/cards/LE_EGR2_TARGETS_DN.html

The pathway delineated by genes up-regulated in the Npy-/-DR compared to the WT-DR are noted by red letters.

Table S5. The list of pathways enriched in genes downregulated in the Npy^{−/−}DR compared to the WT-DR mice.

Pathway Name	P-value	Q-value	Gene	Pathway Description
SEMBA_FHIT_TARGETS_UP	0.0007	0.0740	COL27A1 COL1A1	http://www.broadinstitute.org/gsea/msigdb/cards/SEMBA_FHIT_TARGETS_UP.html
LEE_LIVER_CANCER_MYC_E2F1_UP	0.0009	0.0740	FMO3 CYP39A1 COL1A1	http://www.broadinstitute.org/gsea/msigdb/cards/LEE_LIVER_CANCER_MYC_E2F1_UP.html
LEE_LIVER_CANCER_E2F1_UP	0.0013	0.0740	FMO3 CYP39A1 COL1A1	http://www.broadinstitute.org/gsea/msigdb/cards/LEE_LIVER_CANCER_E2F1_UP.html
DENDRITE	0.0015	0.0740	ACTN2 BNIP3	http://www.broadinstitute.org/gsea/msigdb/cards/DENDRITE.html
REACTOME_PHASE_1_FUNCTIONALIZATION_OF_COMPOUNDS	0.0018	0.0740	FMO2 CYP39A1 FMO3	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME_PHASE_1_FUNCTIONALIZATION_OF_COMPOUNDS.html
GRABARCZYK_BCL11B_TARGETS_UP	0.0028	0.0740	PIK3R1 BNIP3 CAMSAP1L1	http://www.broadinstitute.org/gsea/msigdb/cards/GRABARCZYK_BCL11B_TARGETS_UP.html
NIKOLSKY_BREAST_CANCER_15Q26_AMPLICON	0.0028	0.0740	LRRC28 TTC23	http://www.broadinstitute.org/gsea/msigdb/cards/NIKOLSKY_BREAST_CANCER_15Q26_AMPLICON.html
YAO_TEMPORAL_RESPONSE_TO_PROGESTERONE_CLUSTER_16	0.0029	0.0740	COL1A1 STRA6 PCP4L1	http://www.broadinstitute.org/gsea/msigdb/cards/YAO_TEMPORAL_RESPONSE_TO_PROGESTERONE_CLUSTER_16.html
RADMACHER_AML_PROGNOSIS	0.0029	0.0740	COL1A1 NFIB GYPC	http://www.broadinstitute.org/gsea/msigdb/cards/RADMACHER_AML_PROGNOSIS.html
REACTOME_COLLAGEN_MEDIATED_ACTIVATION_CASCADE	0.0031	0.0740	COL1A1 PIK3R1	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME_COLLAGEN_MEDIATED_ACTIVATION_CASCADE.html
SHI_SPARC_TARGETS_UP	0.0033	0.0740	PIK3R1 ANKRD11	http://www.broadinstitute.org/gsea/msigdb/cards/SHI_SPARC_TARGETS_UP.html
RICKMAN_HEAD_AND_NECK_CANCER_E	0.0038	0.0740	FMO2 CES1 FMO3	http://www.broadinstitute.org/gsea/msigdb/cards/RICKMAN_HEAD_AND_NECK_CANCER_E.html
NAKAMURA_CANCER_MICROENVIRONMENT_UP	0.0039	0.0740	LRRC28 COL1A1	http://www.broadinstitute.org/gsea/msigdb/cards/NAKAMURA_CANCER_MICROENVIRONMENT_UP.html

MONOOXYGENASE_ACTIVITY	0.0049	0.0852	CYP39A1 FMO2	http://www.broadinstitute.org/gsea/msigdb/cards/MONOOXYGENASE_ACTIVITY.html
MARTORIATI_MDM4_TARGETS_NEUROEPITHELIUM_UP	0.0061	0.0992	BNIP3 2410004N09RIK MT1	http://www.broadinstitute.org/gsea/msigdb/cards/MARTORIATI_MDM4_TARGETS_NEUROEPITHELIUM_UP.html
HOOI_ST7_TARGETS_DN	0.0082	0.1019	MCOLN3 COL1A1 PPP1R3B	http://www.broadinstitute.org/gsea/msigdb/cards/HOOI_ST7_TARGETS_DN.html
MICROSOME	0.0096	0.1019	FMO3 CYP39A1	http://www.broadinstitute.org/gsea/msigdb/cards/MICROSOME.html
VESICULAR_FRACTION	0.0105	0.1019	FMO3 CYP39A1	http://www.broadinstitute.org/gsea/msigdb/cards/VESICULAR_FRACTION.html
REACTOME_BIOLOGICAL_OXIDATIONS	0.0108	0.1019	FMO2 CYP39A1 FMO3	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME_BIOLOGICAL_OXIDATIONS.html
LIANG_HEMATOPOIESIS_STEM_CELL_NUMBER_LARGE_VS_TINY_DN	0.0110	0.1019	NPTX1 KLHL7	http://www.broadinstitute.org/gsea/msigdb/cards/LIANG_HEMATOPOIESIS_STEM_CELL_NUMBER_LARGE_VS_TINY_DN.html
SENESE_HDAC2_TARGETS_DN	0.0112	0.1019	COL1A1 ZBTB20 NFIB	http://www.broadinstitute.org/gsea/msigdb/cards/SENESE_HDAC2_TARGETS_DN.html
REACTOME_SIGNALING_BY_EGFR	0.0129	0.1019	PIK3R1 ADAM17	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME_SIGNALING_BY_EGFR.html
INTEGRAL_TO_ORGANELLE_MEMBRANE	0.0135	0.1019	PEX11A BNIP3	http://www.broadinstitute.org/gsea/msigdb/cards/INTEGRAL_TO_ORGANELLE_MEMBRANE.html
KLEIN_PRIMARY_EFFUSION_LYMPHOMA_UP	0.0140	0.1019	NFIB ILF3	http://www.broadinstitute.org/gsea/msigdb/cards/KLEIN_PRIMARY_EFFUSION_LYMPHOMA_UP.html
BOYAUULT_LIVER_CANCER_SUBCLASS_G3_DN	0.0145	0.1019	PIK3R1 ACAT1	http://www.broadinstitute.org/gsea/msigdb/cards/BOYAUULT_LIVER_CANCER_SUBCLASS_G3_DN.html
INTRINSIC_TO_ORGANELLE_MEMBRANE	0.0145	0.1019	PEX11A BNIP3	http://www.broadinstitute.org/gsea/msigdb/cards/INTRINSIC_TO_ORGANELLE_MEMBRANE.html
PROTEIN_COMPLEX_BINDING	0.0162	0.1019	PIK3R1 ACTN2	http://www.broadinstitute.org/gsea/msigdb/cards/PROTEIN_COMPLEX_BINDING.html
BOQUEST_STEM_CELL_CULTURED_VS_FRESH_UP	0.0179	0.1019	FMO3	http://www.broadinstitute.org/gsea/msigdb/cards/BOQUEST_STEM_CELL_CULTURED_VS_FRESH_UP.html
REACTOME_PLATELET_ACTIVATION_TRIGGERS	0.0191	0.1019	PIK3R1 COL1A1	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME_PLATELET_ACTIVATION_TRIGGERS.html

PASQUALUCCI_LYMPHOMA_BY_GC_STAGE_UP	0.0195	0.1019	MT1 PEX11A FNIP2 PLEKHF1	http://www.broadinstitute.org/gsea/msigdb/cards/PASQUALUCCI_LYMPHOMA_BY_GC_STAGE_UP.html
SWEET_LUNG_CANCER_KRAS_DN	0.0209	0.1019	COL1A1 NFIB FMO3 G0S2 ZBTB20	http://www.broadinstitute.org/gsea/msigdb/cards/SWEET_LUNG_CANCER_KRAS_DN.html
KAPOSI_LIVER_CANCER_POOR_SURVIVAL_DN	0.0214	0.1019	PIK3R1	http://www.broadinstitute.org/gsea/msigdb/cards/KAPOSI_LIVER_CANCER_POOR_SURVIVAL_DN.html
REACTOME_PLATELET_ACTIVATION	0.0223	0.1019	PIK3R1 ACTN2 COL1A1	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME_PLATELET_ACTIVATION.html
REACTOME_SIGNALING_BY_PDGF	0.0223	0.1019	PIK3R1 COL1A1	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME_SIGNALING_BY_PDGF.html
SENGUPTA_EBNA1_ANTICORRELATED	0.0226	0.1019	PPP1R3B ACTN2 PLEKHF1	http://www.broadinstitute.org/gsea/msigdb/cards/SENGUPTA_EBNA1_ANTICORRELATED.html
YAMASHITA_METHYLATED_IN_PROSTATE_CANCER	0.0230	0.1019	COL1A1 G0S2	http://www.broadinstitute.org/gsea/msigdb/cards/YAMASHITA_METHYLATED_IN_PROSTATE_CANCER.html
FUNG_IL2_TARGETS_WITH_STAT5_BINDING_SITES	0.0250	0.1019	NOP16	http://www.broadinstitute.org/gsea/msigdb/cards/FUNG_IL2_TARGETS_WITH_STAT5_BINDING_SITES.html
CLAUS_PGR_POSITIVE_MENINGIOMA_UP	0.0250	0.1019	PEX11A	http://www.broadinstitute.org/gsea/msigdb/cards/CLAUS_PGR_POSITIVE_MENINGIOMA_UP.html
BREDEMEYER_RAG_SIGNALING_NOT_VIA_ATM_UP	0.0271	0.1019	KLHL7 DOCK7	http://www.broadinstitute.org/gsea/msigdb/cards/BREDEMEYER_RAG_SIGNALING_NOT_VIA_ATM_UP.html
LEE_LIVER_CANCER_DENA_DN	0.0278	0.1019	PEX11A RORC	http://www.broadinstitute.org/gsea/msigdb/cards/LEE_LIVER_CANCER_DENA_DN.html
KEGG_DRUG_METABOLISM_CYTOCHROME_P450	0.0278	0.1019	FMO2 FMO3	http://www.broadinstitute.org/gsea/msigdb/cards/KEGG_DRUG_METABOLISM_CYTOCHROME_P450.html
NAKAYAMA_SOFT_TISSUE_TUMORS_PCA1_DN	0.0285	0.1019	NFIB LRRN2	http://www.broadinstitute.org/gsea/msigdb/cards/NAKAYAMA_SOFT_TISSUE_TUMORS_PCA1_DN.html
TCGA_GLIOMASTOMA_MUTATED	0.0285	0.1019	PIK3R1	http://www.broadinstitute.org/gsea/msigdb/cards/TCGA_GLIOMASTOMA_MUTATED.html
REACTOME_FORMATION_OF_PLAT	0.0294	0.1019	PIK3R1 ACTN2 COL1A1	http://www.broadinstitute.org/gsea/msigdb/cards/REA

ELET_PLUG				CTOME_FORMATION_OF_PLATELET_PLUG.html
YAMASHITA_LIVER_CANCER_STEM_CELL_DN	0.0299	0.1019	CES1 FMO3	http://www.broadinstitute.org/gsea/msigdb/cards/YAMASHITA_LIVER_CANCER_STEM_CELL_DN.html
FARMER_BREAST_CANCER_APOCRINE_VS_BASAL	0.0309	0.1019	PEX11A PIK3R1 CES1 TMEM87A	http://www.broadinstitute.org/gsea/msigdb/cards/FARMER_BREAST_CANCER_APOCRINE_VS_BASAL.html
HAN_SATB1_TARGETS_DN	0.0312	0.1019	BNIP3 MCOLN3 VPS13C CAMSAP1L1	http://www.broadinstitute.org/gsea/msigdb/cards/HAN_SATB1_TARGETS_DN.html
YAO_TEMPORAL_RESPONSE_TO_PROGESTERONE_CLUSTER_0	0.0314	0.1019	BNIP3 2410004N09RIK	http://www.broadinstitute.org/gsea/msigdb/cards/YAO_TEMPORAL_RESPONSE_TO_PROGESTERONE_CLUSTER_0.html
BENPORATH_ES_CORE_NINE	0.0320	0.1019	ILF3	http://www.broadinstitute.org/gsea/msigdb/cards/BENPORATH_ES_CORE_NINE.html
BERENJENO_TRANSFORMED_BY_RHOA_REVERSIBLY_UP	0.0320	0.1019	PIK3R1	http://www.broadinstitute.org/gsea/msigdb/cards/BERENJENO_TRANSFORMED_BY_RHOA_REVERSIBLY_UP.html
HAEGERSTRAND_RESPONSE_TO_IMATINIB	0.0320	0.1019	COL1A1	http://www.broadinstitute.org/gsea/msigdb/cards/HAEGERSTRAND_RESPONSE_TO_IMATINIB.html
RHEIN_ALL_GLUCOCORTICOID_THERAPY_UP	0.0322	0.1019	ANKRD11 G0S2	http://www.broadinstitute.org/gsea/msigdb/cards/RHEIN_ALL_GLUCOCORTICOID_THERAPY_UP.html
MCBRYAN_PUBERTAL_BREAST_6_7WK_UP	0.0336	0.1019	PIK3R1 ZBTB20 NFIB	http://www.broadinstitute.org/gsea/msigdb/cards/MCBRYAN_PUBERTAL_BREAST_6_7WK_UP.html
NAKAYAMA_SOFT_TISSUE_TUMORS_PCA2_DN	0.0337	0.1019	CES1 G0S2	http://www.broadinstitute.org/gsea/msigdb/cards/NAKAYAMA_SOFT_TISSUE_TUMORS_PCA2_DN.html
LIEB_BREAST_CARCINOMA_METAPLASTIC_VS_DUCTAL_UP	0.0337	0.1019	G0S2 COL27A1	http://www.broadinstitute.org/gsea/msigdb/cards/LIEB_BREAST_CARCINOMA_METAPLASTIC_VS_DUCTAL_UP.html
PAL_PRMT5_TARGETS_UP	0.0340	0.1019	DOCK7 ILF3 NFIB	http://www.broadinstitute.org/gsea/msigdb/cards/PAL_PRMT5_TARGETS_UP.html
HOLLMAN_APOPTOSIS_VIA_CD40_UP	0.0349	0.1019	CYP39A1 ACAT1 NFIB	http://www.broadinstitute.org/gsea/msigdb/cards/HOLLMAN_APOPTOSIS_VIA_CD40_UP.html
FOCAL_ADHESION_FORMATION	0.0355	0.1019	ACTN2	http://www.broadinstitute.org/gsea/msigdb/cards/FOCAL_ADHESION_FORMATION.html

INSULIN LIKE GROWTH FACTOR RECEPTOR BINDING	0.0355	0.1019	PIK3R1	http://www.broadinstitute.org/gsea/msigdb/cards/INSULIN LIKE GROWTH FACTOR RECEPTOR BINDING.html
PROTEIN PHOSPHATASE BINDING	0.0355	0.1019	PIK3R1	http://www.broadinstitute.org/gsea/msigdb/cards/PROTEIN PHOSPHATASE BINDING.html
FUNG IL2 SIGNALING 1	0.0355	0.1019	NOP16	http://www.broadinstitute.org/gsea/msigdb/cards/FUNG IL2 SIGNALING 1.html
REACTOME SYNTHESIS OF BILE ACIDS AND BILE SALTS VIA 24 HYDROXYCHOLESTEROL	0.0355	0.1019	CYP39A1	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME SYNTHESIS OF BILE ACIDS AND BILE SALTS VIA 24 HYDROXYCHOLESTEROL.html
RESPONSE TO TOXIN	0.0355	0.1019	CES1	http://www.broadinstitute.org/gsea/msigdb/cards/RESPONSE TO TOXIN.html
KEGG FOCAL ADHESION	0.0358	0.1019	PIK3R1 ACTN2 COL1A1	http://www.broadinstitute.org/gsea/msigdb/cards/KEGG FOCAL ADHESION.html
HOEBEKE LYMPHOID STEM CELL DN	0.0377	0.1019	KLHL7 NFIB	http://www.broadinstitute.org/gsea/msigdb/cards/HOEBEKE LYMPHOID STEM CELL DN.html
FOCAL ADHESION	0.0390	0.1019	ACTN2	http://www.broadinstitute.org/gsea/msigdb/cards/FOCAL ADHESION.html
REACTOME GAB1 SIGNALOSOME	0.0390	0.1019	PIK3R1	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME GAB1 SIGNALOSOME.html
BILE ACID METABOLIC PROCESS	0.0390	0.1019	CYP39A1	http://www.broadinstitute.org/gsea/msigdb/cards/BILE ACID METABOLIC PROCESS.html
MITOCHONDRIAL MEMBRANE ORGANIZATION AND BIOGENESIS	0.0390	0.1019	BNIP3	http://www.broadinstitute.org/gsea/msigdb/cards/MITOCHONDRIAL MEMBRANE ORGANIZATION AND BIOGENESIS.html
REACTOME REGULATED PROTEOLYSIS OF P75NTR	0.0390	0.1019	ADAM17	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME REGULATED PROTEOLYSIS OF P75NTR.html
ZHANG TARGETS OF EWSR1 FLI1 FUSION	0.0393	0.1019	CES1 G0S2	http://www.broadinstitute.org/gsea/msigdb/cards/ZHANG TARGETS OF EWSR1 FLI1 FUSION.html
COATES MACROPHAGE M1 VS M2 DN	0.0409	0.1019	MCOLN3 BNIP3	http://www.broadinstitute.org/gsea/msigdb/cards/COATES MACROPHAGE M1 VS M2 DN.html
DEFENSE RESPONSE TO VIRUS	0.0424	0.1019	BNIP3	http://www.broadinstitute.org/gsea/msigdb/cards/DEFENSE RESPONSE TO VIRUS.html
MICROBODY MEMBRANE	0.0424	0.1019	PEX11A	http://www.broadinstitute.org/gsea/msigdb/cards/MICROBODY MEMBRANE.html

				ROBODY_MEMBRANE.html
SA_PROGRAMMED_CELL_DEATH	0.0424	0.1019	CES1	http://www.broadinstitute.org/gsea/msigdb/cards/SA_PROGRAMMED_CELL_DEATH.html
PEROXISOMAL_MEMBRANE	0.0424	0.1019	PEX11A	http://www.broadinstitute.org/gsea/msigdb/cards/PEROXISOMAL_MEMBRANE.html
BIOCARTA_TRKA_PATHWAY	0.0424	0.1019	PIK3R1	http://www.broadinstitute.org/gsea/msigdb/cards/BIOCARTA_TRKA_PATHWAY.html
ZHOU_INFLAMMATORY_RESPONSE_FIMA_UP	0.0429	0.1019	ACAT1 ADAM17 TTC23 NOP16 G0S2	http://www.broadinstitute.org/gsea/msigdb/cards/ZHOU_INFLAMMATORY_RESPONSE_FIMA_UP.html
REACTOME_CELL_SURFACE_INTERACTIONS_AT_THE_VASCULAR_WALL	0.0452	0.1019	PIK3R1 COL1A1	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME_CELL_SURFACE_INTERACTIONS_AT_THE_VASCULAR_WALL.html
PEROXISOMAL_PART	0.0459	0.1019	PEX11A	http://www.broadinstitute.org/gsea/msigdb/cards/PEROXISOMAL_PART.html
PHOSPHATASE_BINDING	0.0459	0.1019	PIK3R1	http://www.broadinstitute.org/gsea/msigdb/cards/PHOSPHATASE_BINDING.html
MICROBODY_PART	0.0459	0.1019	PEX11A	http://www.broadinstitute.org/gsea/msigdb/cards/MICROBODY_PART.html
HORMONE_BINDING	0.0459	0.1019	PIK3R1	http://www.broadinstitute.org/gsea/msigdb/cards/HORMONE_BINDING.html
DNA_FRAGMENTATION_DURING_APOPTOSIS	0.0459	0.1019	BNIP3	http://www.broadinstitute.org/gsea/msigdb/cards/DNA_FRAGMENTATION_DURING_APOPTOSIS.html
MOREAUX_MULTIPLE_MYELOMA_BY_TACI_UP	0.0470	0.1019	FMO2 LRRN2 ACTN2 STRA6	http://www.broadinstitute.org/gsea/msigdb/cards/MOREAUX_MULTIPLE_MYELOMA_BY_TACI_UP.html
REACTOME_METABOLISM_OF_LIPIDS_AND_LIPOPROTEINS	0.0490	0.1019	CYP39A1 PEX11A ACAT1	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME_METABOLISM_OF_LIPIDS_AND_LIPOPROTEINS.html
REACTOME_ENDOGENOUS_STEROLS	0.0493	0.1019	CYP39A1	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME_ENDOGENOUS_STEROLS.html
CELL_SUBSTRATE_ADHERENS_JUNCTION	0.0493	0.1019	ACTN2	http://www.broadinstitute.org/gsea/msigdb/cards/CELL_SUBSTRATE_ADHERENS_JUNCTION.html
REACTOME_PLATELET_ADHESION_TO_EXPOSED_COLLAGEN	0.0493	0.1019	COL1A1	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME_PLATELET_ADHESION_TO_EXPOSED_COLLAGEN.html

YAMASHITA_LIVER_CANCER_WITH_EPCAM_DN	0.0493	0.1019	CES1	http://www.broadinstitute.org/gsea/msigdb/cards/YAMASHITA_LIVER_CANCER_WITH_EPCAM_DN.html
BIOCARTA_PS1_PATHWAY	0.0493	0.1019	ADAM17	http://www.broadinstitute.org/gsea/msigdb/cards/BIOCARTA_PS1_PATHWAY.html
PROTEIN_TETRAMERIZATION	0.0493	0.1019	ACTN2	http://www.broadinstitute.org/gsea/msigdb/cards/PROTEIN_TETRAMERIZATION.html
BIOCARTA_CELL2CELL_PATHWAY	0.0493	0.1019	ACTN2	http://www.broadinstitute.org/gsea/msigdb/cards/BIOCARTA_CELL2CELL_PATHWAY.html

The pathways delineated by genes upregulated in the WT-DR compared to the WT-AL mouse liver are noted by red letters.

Table S6. The list of pathways enriched in genes upregulated in the Npy^{-/-}DR compared to the WT-DR mice.

Pathway Name	P-value	Q-value	Gene	Pathway Description
UEDA_PERIFERAL_CLOCK	0.0000	0.0010	ETHE1 AQP8 CRIP2 FDPS GLDC HSD3B5 ID2 S100A10 GABARAPL1	http://www.broadinstitute.org/gsea/msigdb/cards/UEDA_PERIFERAL_CLOCK.html
ICHIBA_GRAFT_VERSUS_HOST_DISEASE_35D_DN	0.0001	0.0213	CYP7B1 HSD3B2 LIFR MUP4 OAT	http://www.broadinstitute.org/gsea/msigdb/cards/ICHIBA_GRAFT_VERSUS_HOST_DISEASE_35D_DN.html
ICHIBA_GRAFT_VERSUS_HOST_DISEASE_D7_DN	0.0004	0.1003	LIFR MUP4 HSD17B2 NRP1	http://www.broadinstitute.org/gsea/msigdb/cards/ICHIBA_GRAFT_VERSUS_HOST_DISEASE_D7_DN.html
LEE_LIVER_CANCER_DENA_UP	0.0006	0.1221	ANXA5 FBLN2 LPL SPP1	http://www.broadinstitute.org/gsea/msigdb/cards/LEE_LIVER_CANCER_DENA_UP.html
CUI_TCF21_TARGETS_UP	0.0016	0.2331	MEG3 COL3A1 CYP7B1	http://www.broadinstitute.org/gsea/msigdb/cards/CUI_TCF21_TARGETS_UP.html
BIOCARTA_LECTIN_PATHWAY	0.0027	0.2331	C6 C9	http://www.broadinstitute.org/gsea/msigdb/cards/BIOCARTA_LECTIN_PATHWAY.html
MODY_HIPPOCAMPUS_NEONATAL	0.0027	0.2331	NRP1 LPL	http://www.broadinstitute.org/gsea/msigdb/cards/MODY_HIPPOCAMPUS_NEONATAL.html
ELLWOOD_MYC_TARGETS_UP	0.0031	0.2331	BAG2 DPP7	http://www.broadinstitute.org/gsea/msigdb/cards/ELLWOOD_MYC_TARGETS_UP.html
CAIRO_LIVER_DEVELOPMENT_DN	0.0031	0.2331	HSD17B2 MORC4 FKBP11 GLDC C9 F11	http://www.broadinstitute.org/gsea/msigdb/cards/CAIRO_LIVER_DEVELOPMENT_DN.html
PARENT_MTOR_SIGNALING_UP	0.0035	0.2331	HSD17B2 TOP3A ETHE1 TSHZ2 F11 RTEL1 CTH GABARAPL1 FDPS PLOD1	http://www.broadinstitute.org/gsea/msigdb/cards/PARENT_MTOR_SIGNALING_UP.html
BIOCARTA_CLASSIC_PATHWAY	0.0036	0.2331	C6 C9	http://www.broadinstitute.org/gsea/msigdb/cards/BIOCARTA_CLASSIC_PATHWAY.html
RODRIGUES_THYROID_CARCINOMA_UP	0.0042	0.2331	FKBP11 SDF2L1	http://www.broadinstitute.org/gsea/msigdb/cards/RODRIGUES_THYROID_CARCINOMA_UP.html

LEE_LIVER_CANCER_MYC_E2F1_UP	0.0050	0.2331	ANXA5 LPL SPP1	http://www.broadinstitute.org/gsea/msigdb/cards/LEE_LIVER_CANCER_MYC_E2F1_UP.html
ZHU_CMV_24_HR_DN	0.0052	0.2331	COL3A1 HSD17B2 ID2	http://www.broadinstitute.org/gsea/msigdb/cards/ZHU_CMV_24_HR_DN.html
KEGG_STEROID_HORMONE_BIOSYNTHESIS	0.0055	0.2331	HSD17B2 CYP7B1 HSD3B2	http://www.broadinstitute.org/gsea/msigdb/cards/KEGG_STEROID_HORMONE_BIOSYNTHESIS.html
JEON_SMAD6_TARGETS_DN	0.0060	0.2331	CTH DDC	http://www.broadinstitute.org/gsea/msigdb/cards/JEON_SMAD6_TARGETS_DN.html
SUH_COEXPRESSED_WITH_ID1_AND_ID2_UP	0.0060	0.2331	GABARAPL1 ID2	http://www.broadinstitute.org/gsea/msigdb/cards/SUH_COEXPRESSED_WITH_ID1_AND_ID2_UP.html
TONG_INTERACT_WITH_PTTG1	0.0061	0.2331	GSTM3 NOB1 GABARAPL1	http://www.broadinstitute.org/gsea/msigdb/cards/TONG_INTERACT_WITH_PTTG1.html
RODWELL_AGING_KIDNEY_DN	0.0063	0.2331	LPL CTH GABARAPL1 OAT	http://www.broadinstitute.org/gsea/msigdb/cards/RODWELL_AGING_KIDNEY_DN.html
DIAZ_CHRONIC_MEYLOGENOUS_LEUKEMIA_DN	0.0065	0.2331	ANXA5 EEF1A1 GAS7 LPL	http://www.broadinstitute.org/gsea/msigdb/cards/DIAZ_CHRONIC_MEYLOGENOUS_LEUKEMIA_DN.html
BIOCARTA_COMP_PATHWAY	0.0067	0.2331	C9 C6	http://www.broadinstitute.org/gsea/msigdb/cards/BIOCARTA_COMP_PATHWAY.html
MARTINEZ_RESPONSE_TO TRABECTEDIN_UP	0.0073	0.2331	ANXA5 S100A10 ID2	http://www.broadinstitute.org/gsea/msigdb/cards/MARTINEZ_RESPONSE_TO TRABECTEDIN_UP.html
WILLERT_WNT_SIGNALING	0.0074	0.2331	GSTM3 ID2	http://www.broadinstitute.org/gsea/msigdb/cards/WILLERT_WNT_SIGNALING.html
GRUETZMANN_PANCREATIC_CANCER_UP	0.0074	0.2331	CKS1B CETN2 EIF4G3 FBLN2 CRIP2 ANXA5 S100A10	http://www.broadinstitute.org/gsea/msigdb/cards/GRUETZMANN_PANCREATIC_CANCER_UP.html
LEE_LIVER_CANCER_MYC_TGFA_DN	0.0077	0.2331	AQP8 CYP7B1 OAT	http://www.broadinstitute.org/gsea/msigdb/cards/LEE_LIVER_CANCER_MYC_TGFA_DN.html
KAN_RESPONSE_TO_ARSENIC_TRIOXIDE	0.0078	0.2331	ID2 GSTM3 CTH GABARAPL1	http://www.broadinstitute.org/gsea/msigdb/cards/KAN_RESPONSE_TO_ARSENIC_TRIOXIDE.html
CAIRO_HEPATOBLASTOMA_DN	0.0078	0.2331	FAM134B CTH ID2 C6 C9 F11	http://www.broadinstitute.org/gsea/msigdb/cards/CAIRO_HEPATOBLASTOMA_DN.html

SETLUR_PROSTATE_CANCER_TMPRS S2_ERG_FUSION_UP	0.0080	0.2331	PEX10 ERG EIF4G3	http://www.broadinstitute.org/gsea/msigdb/cards/SETLUR_PROSTATE_CANCER_TMPRS2_ERG_FUSION_UP.html
SHAFFER_IRF4_TARGETS_IN_ACTIVATED_DENDRITIC_CELL	0.0084	0.2331	FKBP11 GLDC GTF2IRD1	http://www.broadinstitute.org/gsea/msigdb/cards/SHAFFER_IRF4_TARGETS_IN_ACTIVATED_DENDRITIC_CELL.html
REACTOME_SIGNALING_BY_PDGF	0.0084	0.2331	RAPGEF1 COL3A1 SPP1	http://www.broadinstitute.org/gsea/msigdb/cards/REACTOME_SIGNALING_BY_PDGF.html
LEE_LIVER_CANCER_CIPROFIBRATE_DN	0.0088	0.2354	CYP7B1 HSD3B2 OAT	http://www.broadinstitute.org/gsea/msigdb/cards/LEE_LIVER_CANCER_CIPROFIBRATE_DN.html
RODWELL_AGING_KIDNEY_NO_BLOOD_DN	0.0095	0.2458	LPL CTH GABARAPL1 OAT	http://www.broadinstitute.org/gsea/msigdb/cards/RODWELL_AGING_KIDNEY_NO_BLOOD_DN.html
STEROID_BIOSYNTHETIC_PROCESS	0.0097	0.2458	CYP7B1 FDPS	http://www.broadinstitute.org/gsea/msigdb/cards/STEROID_BIOSYNTHETIC_PROCESS.html

The pathway delineated by genes down-regulated in the WT-DR compared to the WT-AL mouse liver is noted by red letters.

Table S7. The list of pathways enriched in up-regulated genes in the WT-DR compared to the WT-AL: Analysis with NCBI BioSystems Database.

PathwayName	Changed Genes	Total Genes	Z score	P-value	Gene ID
Biological oxidations	10	107	9.884	2.E-08	Entrez_Gene:13082,Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098,Entrez_Gene:14262,Entrez_Gene:14864,Entrez_Gene:14867,Entrez_Gene:56050,Entrez_Gene:56362,Entrez_Gene:66447
Drug metabolism - cytochrome P450	8	59	10.961	4.E-08	Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098,Entrez_Gene:14262,Entrez_Gene:14864,Entrez_Gene:14867,Entrez_Gene:337924,Entrez_Gene:66447
Metabolism of xenobiotics by cytochrome P450	7	51	10.323	3.E-07	Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098,Entrez_Gene:14864,Entrez_Gene:14867,Entrez_Gene:337924,Entrez_Gene:66447
Retinol metabolism	6	47	9.174	3.E-06	Entrez_Gene:13082,Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098,Entrez_Gene:19682,Entrez_Gene:337924
nicotine degradation II	5	30	9.72	7.E-06	Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098,Entrez_Gene:14262,Entrez_Gene:21743
Phase I - Functionalization of compounds	6	68	7.398	2.E-05	Entrez_Gene:13082,Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098,Entrez_Gene:14262,Entrez_Gene:56050
Cytochrome P450 - arranged by substrate type	5	53	7.028	9.E-05	Entrez_Gene:13082,Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098,Entrez_Gene:56050
Linoleic acid metabolism	4	36	6.918	3.E-04	Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098,Entrez_Gene:337924
Glutathione conjugation	3	15	8.318	4.E-04	Entrez_Gene:14864,Entrez_Gene:14867,Entrez_Gene:66447
Phase II conjugation	4	40	6.506	4.E-04	Entrez_Gene:14864,Entrez_Gene:14867,Entrez_Gene:56362,Entrez_Gene:66447
Xenobiotics	3	20	7.103	8.E-04	Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098
glutathione-mediated detoxification	3	20	7.103	8.E-04	Entrez_Gene:14864,Entrez_Gene:14867,Entrez_Gene:66447
bupropion degradation	3	22	6.734	1.E-03	Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098
nicotine degradation III	3	24	6.41	1.E-03	Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098
Arachidonic acid metabolism	4	67	4.73	2.E-03	Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098,Entrez_Gene:19215

Glutathione metabolism	3	46	4.338	7.E-03	Entrez_Gene:14864,Entrez_Gene:14867,Entrez_Gene:66447
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The pathways delineated by genes down-regulated in the Npy^{-/-}-DR compared to the WT-DR are noted by red letters.

The pathways with $p < 0.01$ are listed.

Table S8. The list of pathways enriched in down-regulated genes in WT-DR compared to WT-AL: Analysis with NCBI BioSystems Database.

PathwayName	Changed Genes	Total Genes	Z score	P-value	Gene ID
Metabolism of lipids and lipoproteins	13	243	5.612	1.7100E-05	Entrez_Gene:105387,Entrez_Gene:110196,Entrez_Gene:12908,Entrez_Gene:13121,Entrez_Gene:13123,Entrez_Gene:13124,Entrez_Gene:14081,Entrez_Gene:15496,Entrez_Gene:170789,Entrez_Gene:18194,Entrez_Gene:18631,Entrez_Gene:18670,Entrez_Gene:73166
Metabolic pathways	27	983	4.050	8.3200E-05	Entrez_Gene:110196,Entrez_Gene:11656,Entrez_Gene:11761,Entrez_Gene:13121,Entrez_Gene:13124,Entrez_Gene:13850,Entrez_Gene:14081,Entrez_Gene:15490,Entrez_Gene:15496,Entrez_Gene:16828,Entrez_Gene:17436,Entrez_Gene:18194,Entrez_Gene:18263,Entrez_Gene:20019,Entrez_Gene:20441,Entrez_Gene:21990,Entrez_Gene:22018,Entrez_Gene:22235,Entrez_Gene:246277,Entrez_Gene:26938,Entrez_Gene:27402,Entrez_Gene:54447,Entrez_Gene:71519,Entrez_Gene:72054,Entrez_Gene:73166,Entrez_Gene:74147,Entrez_Gene:78390
Steroid biosynthesis	4	17	8.131	1.2327E-04	Entrez_Gene:13121,Entrez_Gene:15490,Entrez_Gene:18194,Entrez_Gene:73166
Cholesterol biosynthesis	4	20	7.420	2.1260E-04	Entrez_Gene:110196,Entrez_Gene:13121,Entrez_Gene:18194,Entrez_Gene:73166
superpathway of cholesterol biosynthesis	4	23	6.848	3.4109E-04	Entrez_Gene:110196,Entrez_Gene:15490,Entrez_Gene:18194,Entrez_Gene:73166
Synthesis of bile acids and bile salts	4	24	6.680	3.9412E-04	Entrez_Gene:105387,Entrez_Gene:13123,Entrez_Gene:13124,Entrez_Gene:170789
cholesterol biosynthesis III (via desmosterol)	3	9	8.524	4.0151E-04	Entrez_Gene:15490,Entrez_Gene:18194,Entrez_Gene:73166
Peroxisome	6	73	5.250	4.6562E-04	Entrez_Gene:12908,Entrez_Gene:13850,Entrez_Gene:14081,Entrez_Gene:170789,Entrez_Gene:18631,Entrez_Gene:74147
cholesterol biosynthesis I	3	10	8.051	5.1719E-04	Entrez_Gene:15490,Entrez_Gene:18194,Entrez_Gene:73166
Synthesis of bile acids and bile salts via 27-hydroxycholesterol	3	11	7.642	6.5222E-04	Entrez_Gene:105387,Entrez_Gene:13123,Entrez_Gene:13124
Cytochrome P450 - arranged by substrate type	5	53	5.258	7.9410E-04	Entrez_Gene:13121,Entrez_Gene:13123,Entrez_Gene:13124,Entrez_Gene:71519,Entrez_Gene:72054

Endogenous sterols	3	12	7.283	8.0783E-04	Entrez_Gene:13121,Entrez_Gene:13123,Entrez_Gene:13124
Bile acid and bile salt metabolism	4	34	5.416	1.2903E-03	Entrez_Gene:105387,Entrez_Gene:13123,Entrez_Gene:13124,Entrez_Gene:170789
Phase 1 - Functionalization of compounds	5	68	4.434	2.2442E-03	Entrez_Gene:13121,Entrez_Gene:13123,Entrez_Gene:13124,Entrez_Gene:71519,Entrez_Gene:72054
Amoebiasis	6	104	4.051	2.6267E-03	Entrez_Gene:11472,Entrez_Gene:12279,Entrez_Gene:18751,Entrez_Gene:20706,Entrez_Gene:226519,Entrez_Gene:381286
Synthesis of bile acids and bile salts via 7alpha-hydroxycholesterol	3	20	5.437	2.9222E-03	Entrez_Gene:105387,Entrez_Gene:13124,Entrez_Gene:170789
Biological oxidations	6	107	3.961	3.0066E-03	Entrez_Gene:13121,Entrez_Gene:13123,Entrez_Gene:13124,Entrez_Gene:22235,Entrez_Gene:71519,Entrez_Gene:72054
Beta-oxidation of very long chain fatty acids	2	5	7.675	3.2199E-03	Entrez_Gene:12908,Entrez_Gene:170789
Terminal pathway of complement	2	6	6.960	4.2578E-03	Entrez_Gene:12274,Entrez_Gene:12279
Miscellaneous substrates	2	7	6.401	5.4293E-03	Entrez_Gene:71519,Entrez_Gene:72054
Beta-oxidation of pristanoyl-CoA	2	8	5.947	6.7309E-03	Entrez_Gene:12908,Entrez_Gene:170789
PPAR signaling pathway	4	61	3.649	9.1366E-03	Entrez_Gene:13124,Entrez_Gene:14081,Entrez_Gene:17436,Entrez_Gene:74147

The pathway delineated by genes up-regulated in the Npy^{-/-}DR compared to the WT-DR are noted by blue letters.

The pathways with p <0.01 are listed.

Table S9. The list of pathways enriched in genes down-regulated in the Npy^{-/-}DR compared to the WT-DR: Analysis with NCBI BioSystems Database.

PathwayName	Changed Genes	Total Genes	Z score	P-value	Gene ID
Phase 1 - Functionalization of compounds	7	68	14.512	2.E-09	Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098,Entrez_Gene:13119,Entrez_Gene:14262,Entrez_Gene:55990,Entrez_Gene:56050
Biological oxidations	7	107	11.354	4.E-08	Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098,Entrez_Gene:13119,Entrez_Gene:14262,Entrez_Gene:55990,Entrez_Gene:56050
nicotine degradation II	5	30	15.799	6.E-08	Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098,Entrez_Gene:14262,Entrez_Gene:55990
Cytochrome P450 - arranged by substrate type	5	53	11.707	8.E-07	Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098,Entrez_Gene:13119,Entrez_Gene:56050
Drug metabolism - cytochrome P450	5	59	11.051	1.E-06	Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098,Entrez_Gene:14262,Entrez_Gene:55990
Retinol metabolism	4	47	9.907	2.E-05	Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098,Entrez_Gene:13119
Xenobiotics	3	20	11.584	5.E-05	Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098
bupropion degradation	3	22	11.021	6.E-05	Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098
Arachidonic acid metabolism	4	67	8.159	7.E-05	Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098,Entrez_Gene:13119
nicotine degradation III	3	24	10.529	8.E-05	Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098
FMO oxidizes nucleophiles	2	3	20.28	1.E-04	Entrez_Gene:14262,Entrez_Gene:55990
Linoleic acid metabolism	3	36	8.483	2.E-04	Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098
Metabolism of xenobiotics by cytochrome P450	3	51	7.008	6.E-04	Entrez_Gene:13096,Entrez_Gene:13097,Entrez_Gene:13098
Fatty acid, triacylglycerol, and ketone body metabolism	3	86	5.182	3.E-03	Entrez_Gene:110446,Entrez_Gene:13119,Entrez_Gene:18631
GPVI-mediated activation cascade	2	27	6.497	4.E-03	Entrez_Gene:12842,Entrez_Gene:18708
Amoebiasis	3	104	4.612	5.E-03	Entrez_Gene:11472,Entrez_Gene:12842,Entrez_Gene:18708
Fatty acid metabolism	2	36	5.542	6.E-03	Entrez_Gene:110446,Entrez_Gene:13119
Metabolism of lipids and lipoproteins	4	243	3.642	7.E-03	Entrez_Gene:110446,Entrez_Gene:13119,Entrez_Gene:18631,Entrez_Gene:56050

Signaling by EGFR	2	44	4.944	9.E-03	Entrez_Gene:11491,Entrez_Gene:18708
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The pathways with $p < 0.01$ are listed.

Table S10. The list of pathways enriched in genes upregulated in the Npy^{-/-}DR compared to the WT-DR: Analysis with NCBI BioSystems Database.

PathwayName	Changed Genes	Total Genes	Z score	P-value	Gene ID
Steroid hormone biosynthesis	4	42	7.297	2.E-04	Entrez_Gene:13123,Entrez_Gene:15486,Entrez_Gene:15493,Entrez_Gene:15496
Mineralocorticoid biosynthesis	2	6	10.14	1.E-03	Entrez_Gene:15493,Entrez_Gene:15496
Terminal pathway of complement	2	6	10.14	1.E-03	Entrez_Gene:12274,Entrez_Gene:12279
Androgen biosynthesis	2	7	9.358	1.E-03	Entrez_Gene:15493,Entrez_Gene:15496
Glucocorticoid biosynthesis	2	8	8.725	2.E-03	Entrez_Gene:15493,Entrez_Gene:15496
Signaling by PDGF	3	60	4.286	7.E-03	Entrez_Gene:107746,Entrez_Gene:12825,Entrez_Gene:20750
Complement cascade	2	19	5.461	7.E-03	Entrez_Gene:12274,Entrez_Gene:12279
Complement and coagulation cascades	3	65	4.069	9.E-03	Entrez_Gene:109821,Entrez_Gene:12274,Entrez_Gene:12279
Metabolism of steroid hormones and vitamins A and D	2	21	5.16	9.E-03	Entrez_Gene:15493,Entrez_Gene:15496

The pathways with $p < 0.01$ are listed.

Table S11. Primer set ID of quantitative RT-PCR

Gene symbol	Gene name	Taqman Expression Assays ID	Gene Takara primer set ID
Primers for hypothalamic neuropeptides			
Npy	neuropeptide Y	Mm03048253_m1	/
Agrp	agouti-related peptide	Mm00475829_g1	/
Pomc	proopiomelanocortin	Mm00435874_m1	/
Ghrh	growth hormone-releasing hormone	Mm01250745_m1	/
Sst	Somatostatin	Mm00436671_m1	/
Primers for Ucp in the brown adipose tissue			
Ucp1	uncouplingp protein 1	Mm01244860_m1	/
Ucp2	uncouplingp protein 2	Mm00627598_m1	/
Ucp3	uncouplingp protein 3	Mm01163394_m1	/
Rn 18s		TaqMan® Ribosomal RNA Control Reagents	/
Primers for selected genes in the liver			
Actb	actin, beta		MA050368
Col27a1	collagen, type XXVII, alpha 1		MA111474

Gypc	glycophorin C		MA113198
Hsd3b2	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 2		MA103166
Hsd3b5	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 5		MA126618
Id2	inhibitor of DNA binding 2		MA106141
Mup4	major urinary protein 4		MA124794
Rn 18s	18S ribosomal RNA		MA050364
Gapdh	glyceraldehyde-3-phosphate dehydrogenase		MA050371
Lpl	lipoprotein lipase		MA120682
Anxa5	annexin A5		MA114909
Lifr	leukemia inhibitory factor receptor		MA120383
Ninj1	ninjurin 1		MA119502
Rorc	RAR-related orphan receptor gamma		MA097596
Fmo3	flavin containing monooxygenase 3		MA108600
S100a10	S100 calcium binding protein A10 (calpactin)		MA108600
Spp1A	secreted phosphoprotein 1		MA130294

Spp1B	secreted phosphoprotein 1		MA114392
EEF1a	eukaryotic translation elongation factor 1 alpha 1		MA080227
Fbln2	fibulin 2		MA128665
Pex11a	peroxisomal biogenesis factor 11 alpha		MA117235

