Supplement Material

Bioinformatic Analysis of Gene Sets Regulated by Ligand-Activated and Dominant-Negative PPARγ in Mouse Aorta

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Supplemental Methods

Analysis of Gene Expression Microarray Datasets:

The microarrays datasets used in the present manuscript are listed below. The top two datasets were generated in the Sigmund laboratory; the others were downloaded from publicly available repositories including NCBI's Gene Expression Omnibus (GEO, http://ncbi.nih.gov/geo) and EBI's Array Express (http://www.ebi.ac.uk/microarray-as/ae/).

Analysis Description	Tissue	Samples	Array Platform	Array Accession	Analysis Method
Rosiglitazone treatment of mice	Thoracic aorta	control (n=3), low2d (n=3), low14d (n=3), high2d (n=3), high14d (n=2)	GPL1261	GSE8949	RMA-Limma
Dominant negative P465L PPARγ mice	Thoracic aorta	control (n=3), dominant negative (n=3)	GPL1261	GSE8949	RMA-Limma
Rosiglitazone treatment of 3T3L1 cells	3T3-L1 cells	control (n=3), rosiglitazone (n=3)	GPL81	GSE1458	MAS5 P/A calls and fold change
Genes expressed in 3T3-L1 cells	3T3-L1 cells	control (n=7)	GPL1261	GSE14004, GSE8682	MAS5 P/A calls
Correlation across multiple human tissues	Various	total hybridizations (n=53)	GPL570	Affymetrix-no accession	RMA-Pearson correlation

All of the above datasets were generated using commercially-available Affymetrix microarray platforms. Mapping of probe set identifiers to gene specific information (e.g., official gene symbol, gene description) was performed using microarray annotation files available from Affymetrix (http://www.affymetrix.com). Annotation files (CSV format) were converted into plain text, parsed and imported into customized MySql (http://www.mysql.com/) databases. For the datasets generated in our laboratory, the data was analyzed using R statistical software (http://www.r-project.org/) and downloaded packages from the associated Bioconductor project (http://www.bioconductor.org). The raw microarray data (i.e., the *.CEL files) was imported into R and normalized using Robust Multi-array Average (RMA).[1] The quality of the array hybridizations was confirmed by utilizing the array quality control (QC) functions in Bioconductor.

Differential expression of genes between groups and their corresponding genetically matched or vehicle treated controls was determined using the Linear Models for Microarray Analysis (limma) package. The adjusted p-value representing statistical significance was determined by analysis of the Affymetrix control probes as described by Smyth.[2]

For the 3T3-L1 adipocyte datasets (GSE1458, GSE14004, and GSE8682), the Affymetrix Microarray Array Suite version 5 algorithm (MAS5) generated signal values and present/absent (P/A) calls were extracted from the publicly available series files. The dataset used to compare gene expression patterns across multiple diverse human tissue samples was downloaded from (http://www.affymetrix.com/support/technical/sample_data/exon_array_data.affx), and analyzed using Affymetrix Power Tools (APT). Using APT default parameters, RMA was used for normalization of the raw data and generation of signal values. The human tissues included in this dataset include breast, cerebellum, heart, kidney, liver, muscle, pancreas, prostate, spleen, testes, and thyroid. Pearson's correlation coefficient (r), computed using customized software written in the Perl programming language (version 5.8.8 for Windows), was used to assess similarity of expression patterns between different genes.

Gene Set Enrichment Analysis

Determination of whether expression of a set of genes, as a group, was statistically changed was accomplished using the JAVA-based command line version of the Gene Set Enrichment Analysis tool (GSEA, http://www.broad.mit.edu/gsea/).[3] For GSEA, the number of gene set permutations was set at 1000, and a p-value less than 0.05 was considered statistically significant. This p-value is the GSEA nominal p-value. This is a permutation derived p-value and does not take into account multiple hypothesis testing. To address multiple testing, we used the R package q-value to calculate a false discovery rate (FDR).[4] For a nominal p-value of 0.05, the estimated FDR was 0.17, which is in line with the threshold (FDR < 0.25) previously suggested for gene set analysis.[3] Also, it should be noted, that for most of our comparisons, we are querying for gene sets that are significantly enriched at a p-value less than 0.05 in multiple datasets (e.g., 4 rosiglitazone treatment groups). The gene sets used in the manuscript and their sources are listed below.

Gene set description	Number Sets	Source
Known PPARγ targets	1	compiled from published literature (http://www.pubmed.gov)
UniProt Knowledgebase	443	http://www.uniprot.org/
Gene Ontology	2014	http://www.geneontology.org
Rosiglitazone induced genes in 3T3-L1 cells	6	GSE1458

The set of known PPARγ target genes was assembled from the literature as follows. We initially searched the NCBI Pubmed database using the keywords “PPRE” and “PPAR gamma”. Inclusion criteria was evidence of at least two of the following 1) up-regulation of endogenous gene expression with thiazolidinedione (TZD) treatment, 2) PPARγ mediated activation of promoter-reporter constructs in transient transfection assays, 3) binding of PPARγ protein to gene promoter in chromatin immunoprecipitation assay (ChIP), or 4) binding of PPARγ to identified PPAR response element (PPRE) in electromobility shift assay (EMSA). During our search, we identified a previously compiled list of PPREs from Lemay et al.[1] Most of the target genes from that study met our criteria and were included in our final list.

Computational search for PPAR response elements:

Genomic sequence (5 kb upstream of the transcriptional start site) from the reference sequence (refseq) database was downloaded from UCSC (http://genome.ucsc.edu) for mouse (March 2005 release, mm6, 18176 sequences). We used a list of experimentally verified PPAR response elements (PPREs) compiled previously to form a position weight matrix.[5] This matrix described the normal sequence variability occurring in PPREs and was used to score potential matches to query sequences. Query sequences achieving a score of 80% of the maximum score, where the maximum score is that derived from the consensus sequence, were considered to be PPREs. This search was implemented using custom software written in Perl. The exact genomic location of each PPRE was determined to ensure that the same PPRE was not counted multiple times.

Analysis of PPARγ binding sites identified in 3T3-L1 adipocytes

In addition to the computational strategy described above, we used a publicly available dataset (Table 1 of Supplemental Materials for manuscript referenced below) mapping the location of PPARγ binding sites in 3T3-L1 adipocytes on the basis of function (chromatin immunoprecipitation and microarray hybridization, ChIP-chip) not computational prediction.[6] A total of 5299 genomic regions binding PPARγ were identified. Independent ChIP assays using quantitative PCR and custom microarrays demonstrated that the false discovery rate for this ChIP-chip experiment was low (3-4%). To merge datasets, we limited our analysis to those genes that were consistently expressed in both aorta and 3T3-L1 adipocytes (3T3-L1 expression data, NCBI GEO Accession Numbers GSE14004 and GSE8682). Mapping of PPARγ binding sites relative to gene location was accomplished using the refLink and refGene tables (assembly mm8) from UCSC (http://genome.ucsc.edu). The p-value for enrichment was determined using Fisher's exact test (one-sided) comparing the proportion of genes with an associated PPRE compared to the proportion in the baseline group (i.e., all genes expressed in 3T3-L1 cells and aorta). Fisher's test was performed using the R statistical package.

Other Informatics:

Functional categorization of genes including mapping to Gene Ontology (GO) terms and statistical tests of term enrichment (modified Fisher's Exact test) was performed using the Database for Annotation, Visualization, and Integrated Discovery (DAVID, http://david.abcc.ncifcrf.gov/) available at the NIH.[7]

References

(1) Lemay DG, Hwang DH. Genome-wide identification of peroxisome proliferator response elements using integrated computational genomics. *J.Lipid Res.* 2006;47:1583-1587.

(2) Smyth GK. Limma: Linear models for microarray data. In: Gentleman RC, Carey VJ, Dudoit S, Irizarry R, Huber W, editors. *Bioinformatics and Computational Biology Solutions using R and Bioconductor*.New York: Springer; 2005. p. 397-420.

(3) Subramanian A, Tamayo P, Mootha VK, Mukherjee S, Ebert BL, Gillette MA, Paulovich A, Pomeroy SL, Golub TR, Lander ES, Mesirov JP. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc.Natl.Acad.Sci.U.S.A.* 2005;102:15545-15550.

(4) Storey JD, Tibshirani R. Statistical significance for genomewide studies. *Proc.Natl.Acad.Sci.U.S.A.* 2003;100:9440-9445.

(5) Keen HL, Ryan MJ, Beyer A, Mathur S, Scheetz TE, Gackle BD, Faraci FM, Casavant TL, Sigmund CD. Gene expression profiling of potential PPAR{gamma} target genes in mouse aorta. *Physiological Genomics.* 2004;18:33-42.

(6) Lefterova MI, Zhang Y, Steger DJ, Schupp M, Schug J, Cristancho A, Feng D, Zhuo D, Stoeckert CJ, Jr., Liu XS, Lazar MA. PPARgamma and C/EBP factors orchestrate adipocyte biology via adjacent binding on a genome-wide scale. *Genes Dev.* 2008;22:2941-2952.

(7) Huang dW, Sherman BT, Tan Q, Kir J, Liu D, Bryant D, Guo Y, Stephens R, Baseler MW, Lane HC, Lempicki RA. DAVID Bioinformatics Resources: expanded annotation database and novel algorithms to better extract biology from large gene lists. *Nucleic Acids Res.* 2007;35:W169-W175.

Supplemental Figures

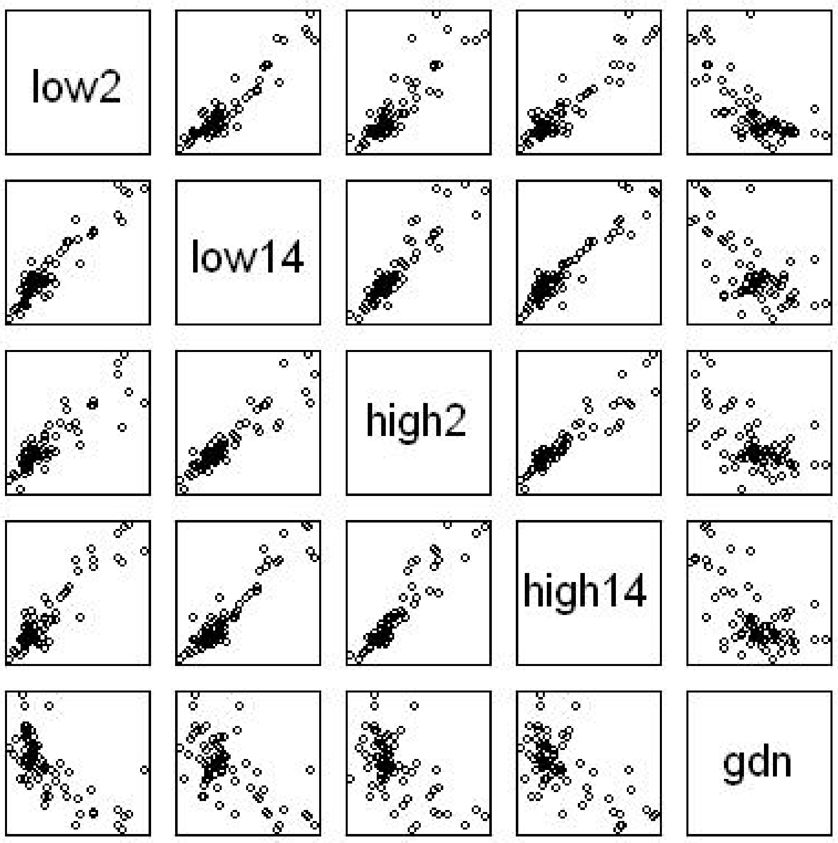

Figure S1. Multiple scatterplots of fold-changes in expression of known PPARγ target genes (Supplemental Table 1) relative to the appropriate control group. All pairwise comparisons are displayed. Mice received rosiglitazone at either a low (3 mg/kg/day) or high (10 mg/kg/day) dose for either 2 or 14 d. For comparisons between different rosiglitazone treatment groups there is a strong positive correlation ($r > 0.9$), whereas there is an inverse or negative correlation ($r < -0.6$) between the rosiglitazone and dominant negative PPARγ group (g-dn).

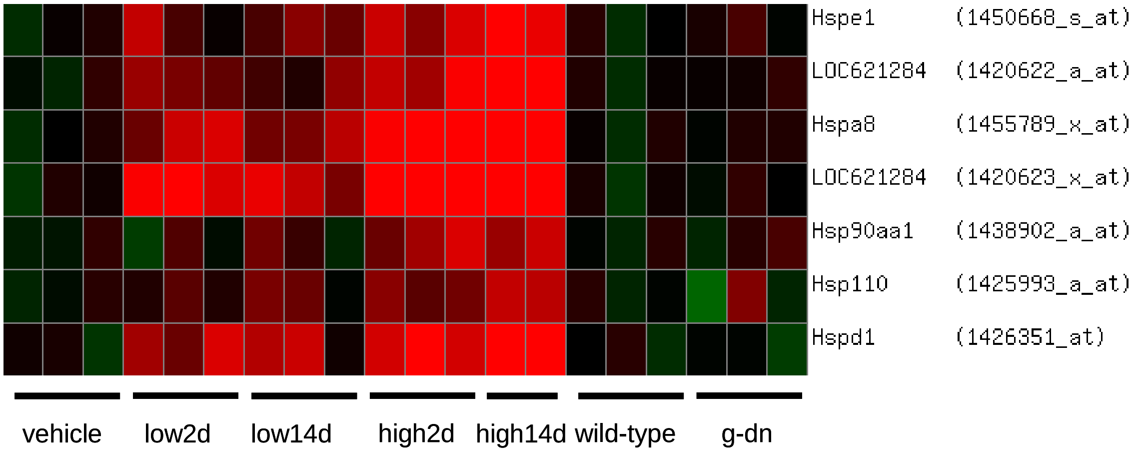

Figure S2. Heat shock proteins displaying rosiglitazone specific activation. All gene expression values have been log2 transformed and normalized to the appropriate control group. Wild-type littermates serve as control for the gene-targeted mice containing a dominant negative isoform of PPARγ (g-dn). Vehicle-treated mice are the control for mice receiving rosiglitazone, a high affinity ligand of PPARγ. Mice received rosiglitazone at either a low (3 mg/kg/day) or high (10 mg/kg/day) dose for either 2 or 14 d. Each column represents a sample, and each row represents a gene. Increasing intensity of red or green color indicates greater up- or down- regulation, respectively, relative to the appropriate control group. Black indicates no change in expression. The genes displayed in this heatmap map to the gene ontology category heat shock protein activity (GO:0003773), were up-regulated by rosiglitazone treatment (significant in at least one experimental group) and did not change (lack of significance and less than 10% change from control group) in the g-dn mice.

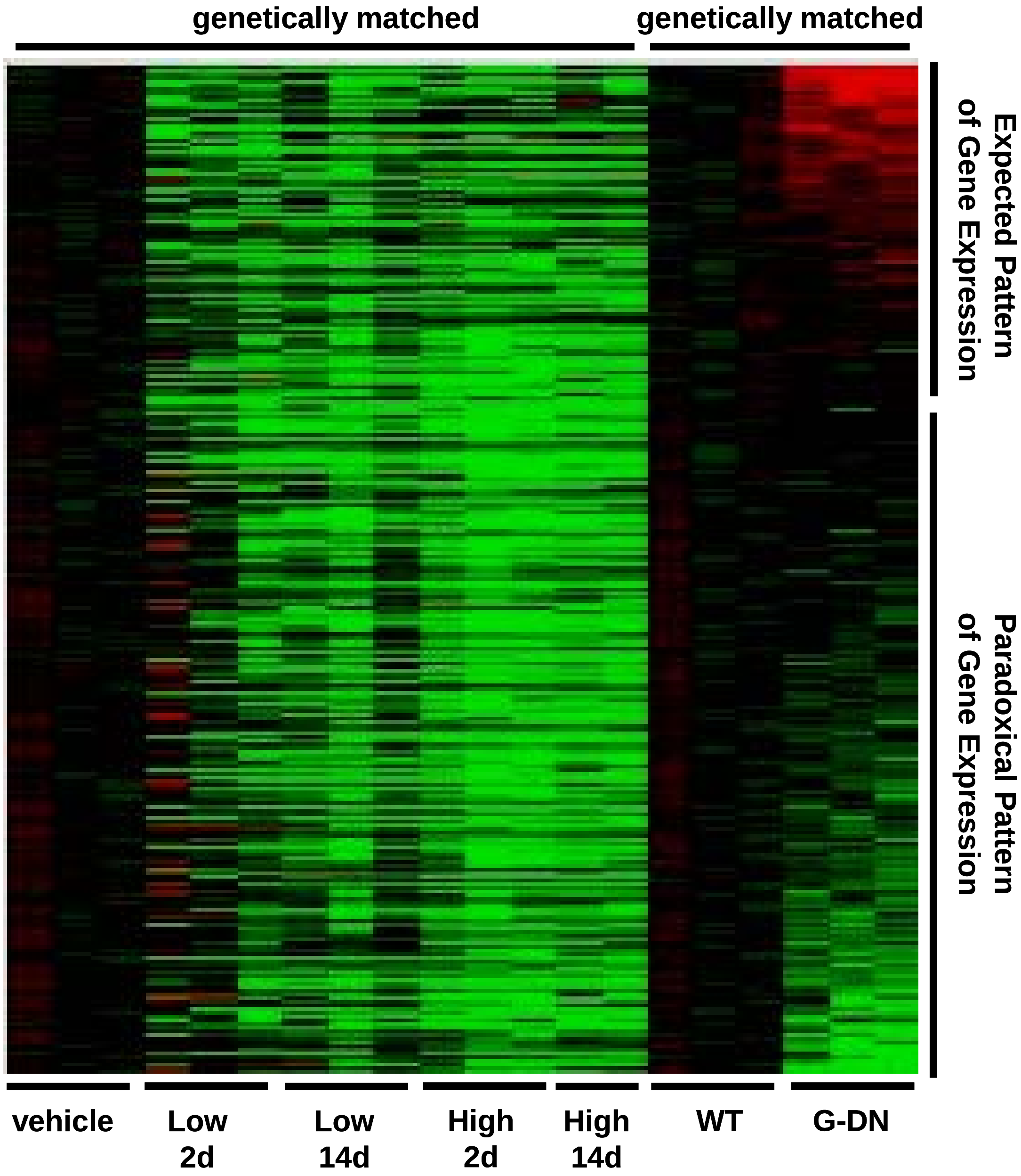

Figure S3. Expression clustering of genes down-regulated in at least one rosiglitazone treatment group. All gene expression values have been log2 transformed and normalized to the appropriate control group. Wild-type littermates serve as control for the gene-targeted mice containing a dominant negative isoform of PPARγ (g-dn). Vehicle-treated mice are the control for mice receiving rosiglitazone, a high affinity ligand of PPARγ. Mice received rosiglitazone at either a low (3 mg/kg/day) or high (10 mg/kg/day) dose for either 2 or 14 d. Each column represents a sample, and each row represents a gene. Increasing intensity of red or green color indicates greater up- or down- regulation, respectively, relative to the appropriate control group. Black indicates no change in expression.

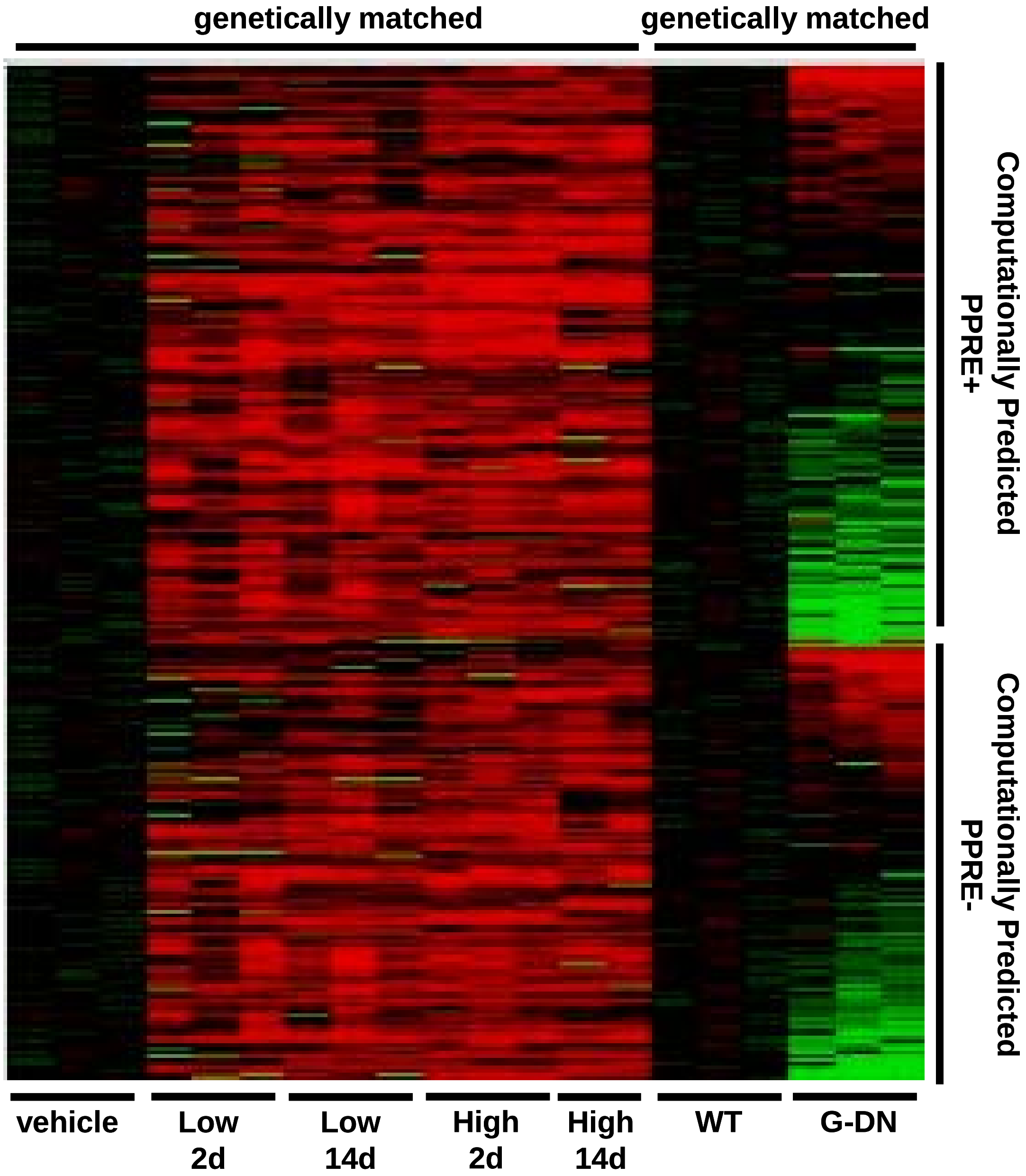

Figure S4. Expression clustering of genes up-regulated in at least one rosiglitazone treatment group sorted by the presence or absence of a computationally identified PPAR response element (PPRE). Analysis was performed as in Supplemental Figure 3.

Supplemental Table 1. Known PPAR gamma target genes.

Gene	Gene ID	Description	PubMed ID	Function
ADFP	11520	adipose differentiation related protein	16197558	lipid metabolism, transport
ADIPOQ	11450	adiponectin, C1Q and collagen domain containing	12829629	lipid metabolism, transport
ANGPTL4	57875	angiopoietin-like 4	15190076	lipid metabolism
APOE	11816	apolipoprotein E	11439103	lipid metabolism, transport
AQP7	11832	aquaporin 7	11679588;11952783	transport
BCMO1	63857	beta-carotene 15,15'-monooxygenase	12759335	oxidoreductase activity
CAT	12359	catalase	12456800	transport, oxidoreductase activity
CD36	12491	CD36 antigen	11716758	transport, cell adhesion
CIDEA	12683	cell death-inducing DNA fragmentation factor, alpha subunit-like effector A	17462989	lipid metabolism
CPT1A	12894	carnitine palmitoyltransferase 1a, liver	17062566	lipid metabolism, transport
DBI	13167	diazepam binding inhibitor	12015306	transport
FABP4	11770	fatty acid binding protein 4, adipocyte	12821652;15273253	transport, lipid binding
G0S2	14373	G0/G1 switch gene 2	16086669	cell cycle
GCK	103988	glucokinase	11872666;14749268	glucose metabolism
IGFBP1	16006	insulin-like growth factor binding protein 1	17062566	growth factor binding
IGFBP2	16008	insulin-like growth factor binding protein 2	17062566	growth factor binding
IGFBP5	16011	insulin-like growth factor binding protein 5	17062566	growth factor binding
INSIG1	231070	insulin induced gene 1	15073165	protein binding
LPL	16956	lipoprotein lipase	8895578;9535723	lipid metabolism
LRP1	16971	low density lipoprotein receptor-related protein 1	12551936	transport
MC2R	17200	melanocortin 2 receptor	15028712	G-protein coupled receptor activity
NPHS1	54631	nephrosis 1 homolog, nephrin (human)	16687628	transferase activity
NR1D1	217166	nuclear receptor subfamily 1, group D, member 1	12821652	transcription factor activity
NR1H3	22259	nuclear receptor subfamily 1, group H, member 3	11604492	lipid metabolism, transport, transcription factor activity
PCK1	18534	phosphoenolpyruvate carboxykinase 1, cytosolic	10224131;11399762	lipid metabolism
PLIN	103968	perilipin	14726448;14729975	lipid metabolism
PTGS2	19225	prostaglandin-endoperoxide synthase 2	11809750	lipid metabolism, prostaglandin biosynthesis

Supplemental Table 1. Known PPAR gamma target genes.

Gene	Gene ID	Description	PubMed ID	Function
SCARB1	20778	scavenger receptor class B, member 1	12763030	cell adhesion
SCNN1G	20278	sodium channel, nonvoltage-gated 1 gamma	16007095	transport
SERPINE1	18787	serine (or cysteine) peptidase inhibitor, clade E, member 1	16843437	plasminogen activator activity
SLC1A2	20511	solute carrier family 1 (glial high affinity glutamate transporter), member 2	17213861	transport
SLC22A1	20517	solute carrier family 22 (organic cation transporter), member 1	15458920	transport
SLC27A1	26457	solute carrier family 27 (fatty acid transporter), member 1	9933587	lipid metabolism, transport
SLC2A2	20526	solute carrier family 2 (facilitated glucose transporter), member 2	10969836;15886523	transport
SORBS1	20411	sorbin and SH3 domain containing 1	10734046	transport
TFF2	21785	trefoil factor 2 (spasmolytic protein 1)	17118693	defense response
UCP1	22227	uncoupling protein 1 (mitochondrial, proton carrier)	11050084;8668156	transport

Supplemental Table 2. Expression changes of known PPAR gamma target genes during rosiglitazone treatments and in mice containing a dominant negative PPAR gamma (G-DN). Red or green represents statistically significant up- or down- regulation, respectively.

ProbeSetID	low2d	low14d	high2d	high14d	g-dn	Gene	Gene ID	Description
1423439_at	2.78	2.28	2.15	3.13	0.59	Pck1	18534	phosphoenolpyruvate carboxykinase 1, cytosolic
1450884_at	2.71	2.29	2.75	3.09	0.58	Cd36	12491	CD36 antigen
1424155_at	2.60	1.98	2.61	2.99	0.63	Fabp4	11770	fatty acid binding protein 4, adipocyte
1425809_at	2.12	1.74	1.94	2.70	0.76	Fabp4	11770	fatty acid binding protein 4, adipocyte
1417130_s_at	3.04	2.33	1.96	2.63	0.88	Angptl4	57875	angiopoietin-like 4
1418197_at	2.60	2.37	2.43	2.50	0.52	Ucp1	22227	uncoupling protein 1 (mitochondrial, proton carrier)
1423166_at	2.18	1.79	2.01	2.49	0.60	Cd36	12491	CD36 antigen
1417956_at	1.86	1.92	1.64	2.48	0.52	Cidea	12683	cell death-inducing DNA fragmentation factor, alpha subunit-like effector A
1439617_s_at	2.65	1.89	1.56	2.44	0.50	Pck1	18534	phosphoenolpyruvate carboxykinase 1, cytosolic
1450883_a_at	2.15	1.75	1.91	2.36	0.61	Cd36	12491	CD36 antigen
1418848_at	1.90	1.67	1.50	2.26	0.69	Aqp7	11832	aquaporin 7
1422651_at	1.76	1.64	1.57	1.98	0.87	Adipoq	11450	adiponectin, C1Q and collagen domain containing
1417023_a_at	1.71	1.64	1.86	1.90	0.71	Fabp4	11770	fatty acid binding protein 4, adipocyte
1451263_a_at	1.67	1.57	1.98	1.85	0.77	Fabp4	11770	fatty acid binding protein 4, adipocyte
1448700_at	1.32	1.18	1.43	1.79	0.66	G0s2	14373	G0/G1 switch gene 2
1415904_at	1.59	1.51	1.64	1.75	0.93	Lpl	16956	lipoprotein lipase
1419149_at	1.39	1.43	1.60	1.65	1.30	Serpine1	18787	serine (or cysteine) peptidase inhibitor, clade E, member 1
1443983_at	1.08	1.40	1.39	1.54	1.14	Sorbs1	20411	Sorbin and SH3 domain containing 1
1422432_at	1.50	1.36	1.43	1.48	0.81	Dbi	13167	diazepam binding inhibitor
1440311_at	0.97	1.23	1.25	1.47	1.10	Sorbs1	20411	sorbin and SH3 domain containing 1
1418849_x_at	1.92	1.37	1.27	1.41	0.60	Aqp7	11832	aquaporin 7
1438093_x_at	1.32	1.34	1.45	1.40	0.89	Dbi	13167	diazepam binding inhibitor
1417262_at	1.02	0.84	1.15	1.39	1.12	Ptgs2	19225	prostaglandin-endoperoxide synthase 2
1436737_a_at	1.14	1.06	1.28	1.39	1.05	Sorbs1	20411	sorbin and SH3 domain containing 1
1416429_a_at	1.31	1.10	1.33	1.36	0.91	Cat	12359	catalase
1455820_x_at	1.43	1.19	1.18	1.36	0.89	Scarb1	20778	scavenger receptor class B, member 1
1437378_x_at	1.52	1.12	1.14	1.35	0.85	Scarb1	20778	scavenger receptor class B, member 1
1433991_x_at	1.32	1.23	1.34	1.34	0.91	Dbi	13167	diazepam binding inhibitor
1455976_x_at	1.24	1.19	1.28	1.28	0.87	Dbi	13167	diazepam binding inhibitor
1448318_at	1.37	1.14	1.03	1.26	0.77	Adfp	11520	adipose differentiation related protein
1455967_at	1.04	1.17	1.19	1.23	0.98	Sorbs1	20411	sorbin and SH3 domain containing 1

Supplemental Table 2. Expression changes of known PPAR gamma target genes during rosiglitazone treatments and in mice containing a dominant negative PPAR gamma (G-DN). Red or green represents statistically significant up- or down- regulation, respectively.

ProbeSetID	low2d	low14d	high2d	high14d	g-dn	Gene	Gene ID	Description
1441413_at	1.11	1.23	1.15	1.23	0.97	Cat	12359	Catalase
1428471_at	0.96	0.99	1.16	1.21	1.02	Sorbs1	20411	sorbin and SH3 domain containing 1
1416050_a_at	1.33	1.10	1.11	1.20	0.90	Scarb1	20778	scavenger receptor class B, member 1
1433094_at	0.98	1.07	1.06	1.18	0.92	Slc1a2	20511	solute carrier family 1 (glial high affinity glutamate transporter), member 2
1425826_a_at	1.07	1.04	1.05	1.17	0.86	Sorbs1	20411	sorbin and SH3 domain containing 1
1449907_at	1.08	1.23	1.15	1.12	0.98	Bcmo1	63857	beta-carotene 15,15'-monooxygenase
1449067_at	1.14	1.00	1.07	1.12	0.91	Slc2a2	20526	solute carrier family 2 (facilitated glucose transporter), member 2
1422142_at	1.09	1.13	1.16	1.12	0.93	Nphs1	54631	nephrosis 1 homolog, nephrin (human)
1419146_a_at	1.22	1.06	1.10	1.10	1.04	Gck	103988	glucokinase
1418918_at	1.13	1.16	1.12	1.10	1.10	Igfbp1	16006	insulin-like growth factor binding protein 1
1416430_at	1.22	1.03	1.13	1.09	0.82	Cat	12359	catalase
1417263_at	1.02	0.95	0.93	1.09	1.14	Ptgs2	19225	prostaglandin-endoperoxide synthase 2
1442401_at	1.13	1.19	1.19	1.07	0.92	Sorbs1	20411	Sorbin and SH3 domain containing 1
1417358_s_at	0.97	0.99	1.04	1.06	0.82	Sorbs1	20411	sorbin and SH3 domain containing 1
1459763_at	1.05	1.13	1.03	1.05	1.04	Adipoq	11450	Adiponectin, C1Q and collagen domain containing
1458314_at	1.04	1.13	1.10	1.05	0.92	Slc1a2	20511	Solute carrier family 1 (glial high affinity glutamate transporter), member 2
1422448_at	0.99	1.14	1.05	1.04	0.94	Tff2	21785	trefoil factor 2 (spasmolytic protein 1)
1432466_a_at	1.07	1.04	0.83	1.03	0.90	Apoe	11816	apolipoprotein E
1422926_at	1.05	0.97	0.94	1.03	1.05	Mc2r	17200	melanocortin 2 receptor
1419079_at	1.30	1.13	1.19	1.03	0.94	Scnn1g	20278	sodium channel, nonvoltage-gated 1 gamma
1450444_a_at	1.06	0.97	0.91	1.03	0.79	Nr1h3	22259	nuclear receptor subfamily 1, group H, member 3
1446993_at	0.99	1.01	1.00	1.01	0.92	Plin	103968	Perilipin
1434866_x_at	0.99	0.83	0.93	1.00	1.30	Cpt1a	12894	carnitine palmitoyltransferase 1a, liver
1451627_a_at	1.04	1.12	0.97	1.00	0.97	Slc1a2	20511	solute carrier family 1 (glial high affinity glutamate transporter), member 2
1453410_at	1.10	1.10	1.02	0.97	1.06	Angptl4	57875	angiopoietin-like 4
1455209_at	1.17	1.17	1.10	0.97	1.03	Pck1	18534	Phosphoenolpyruvate carboxykinase 1, cytosolic
1438156_x_at	0.94	0.87	0.94	0.96	1.37	Cpt1a	12894	carnitine palmitoyltransferase 1a, liver
1425303_at	0.90	1.03	1.04	0.96	0.94	Gck	103988	glucokinase
1418118_at	1.02	0.99	0.95	0.95	1.18	Slc22a1	20517	solute carrier family 22 (organic cation transporter), member 1
1426464_at	1.20	1.25	1.00	0.95	0.97	Nr1d1	217166	nuclear receptor subfamily 1, group D, member 1
1435658_at	1.38	0.96	1.13	0.94	0.71	Slc27a1	26457	solute carrier family 27 (fatty acid transporter), member 1

Supplemental Table 2. Expression changes of known PPAR gamma target genes during rosiglitazone treatments and in mice containing a dominant negative PPAR gamma (G-DN). Red or green represents statistically significant up- or down- regulation, respectively.

ProbeSetID	**low2d**	**low14d**	**high2d**	**high14d**	**g-dn**	**Gene**	**Gene ID**	**Description**
1442849_at	0.97	0.88	0.98	0.93	1.15	Lrp1	16971	low density lipoprotein receptor-related protein 1
1447582_x_at	1.01	1.08	1.02	0.90	1.09	Adipoq	11450	Adiponectin, C1Q and collagen domain containing
1454671_at	1.22	1.03	1.11	0.90	0.88	Insig1	231070	insulin induced gene 1
1448655_at	0.98	0.92	0.88	0.85	0.96	Lrp1	16971	low density lipoprotein receptor-related protein 1
1422811_at	1.33	0.94	0.88	0.83	0.71	Slc27a1	26457	solute carrier family 27 (fatty acid transporter), member 1
1460409_at	0.99	0.85	0.80	0.78	1.17	Cpt1a	12894	carnitine palmitoyltransferase 1a, liver
1422313_a_at	0.79	0.76	0.79	0.76	0.98	Igfbp5	16011	insulin-like growth factor binding protein 5
1454159_a_at	0.91	0.72	0.55	0.68	0.82	Igfbp2	16008	insulin-like growth factor binding protein 2
1452114_s_at	0.72	0.67	0.68	0.62	1.03	Igfbp5	16011	insulin-like growth factor binding protein 5

Supplemental Table 3. Normalized enrichment values from GSEA analysis using sets of genes responsive to rosiglitazone in adipocytes. Top refers to expressed genes showing the largest fold changes compared to control samples. Red or green represents statistically significant up- or down- regulation, respectively.

Gene Set	**low2d**	**low14d**	**high2d**	**high14d**	**g-dn**
Top-25	2.09	1.48	1.27	1.51	-1.47
Top-50	2.19	1.48	1.49	1.73	-1.85
Top-75	2.32	1.58	1.38	1.87	-1.77
Top-100	2.14	1.44	1.35	1.85	-1.67
Top-125	2.04	1.40	1.36	1.73	-1.79
Top-150	1.98	1.37	1.26	1.76	-1.81
Random-50	0.67	-0.80	-1.28	0.82	0.86

Supplemental Table 4. Normalized enrichment values from GSEA analysis using sets of genes from Gene Ontology (GO) or the UniProt knowledgebase (KW). Red or green represents statistically significant up- or down- regulation, respectively.

GeneSet	low2d	low14d	high2d	high14d	g-dn
GO ; fatty acid metabolic process ; 0006631	2.47	1.67	1.46	2.12	-2.37
GO ; acetyl-CoA C-acyltransferase activity ; 0003988	1.88	1.86	1.50	2.05	-1.90
KW ; Chylomicron	1.93	1.61	1.61	1.85	-1.81
GO ; chylomicron ; 0042627	1.81	1.76	1.74	1.79	-1.71
GO ; signal peptidase activity ; 0009003	2.13	1.74	1.77	2.04	-1.70
GO ; water channel activity ; 0015250	1.70	1.77	1.71	1.70	-1.69
GO ; mitochondrial respiratory chain ; 0005746	2.06	1.67	1.61	1.93	-1.69
GO ; water transport ; 0006833	1.66	1.70	1.66	1.72	-1.68
GO ; G-protein activated inward rectifier potassium channel activity ; 0015467	1.81	1.69	1.81	1.53	-1.67
GO ; extracellular region ; 0005576	1.63	1.40	1.41	1.26	-1.65
KW ; Ionic channel	1.48	1.63	1.64	1.42	-1.64
KW ; VLDL	1.98	1.80	1.72	2.07	-1.64
GO ; serotonin receptor activity ; 0004993	1.68	1.88	1.76	1.60	-1.63
GO ; sodium ion binding ; 0031402	2.12	1.46	1.60	1.72	-1.62
GO ; trypsin activity ; 0004295	1.68	1.62	1.50	1.56	-1.62
GO ; voltage-gated ion channel activity ; 0005244	1.43	1.42	1.36	1.29	-1.61
KW ; Amidation	1.83	1.97	1.98	2.05	-1.60
KW ; Voltage-gated channel	1.47	1.51	1.41	1.42	-1.60
GO ; rhodopsin-like receptor activity ; 0001584	1.83	1.89	1.96	1.51	-1.60
KW ; G-protein coupled receptor	1.78	1.78	1.79	1.47	-1.58
GO ; ion channel activity ; 0005216	1.51	1.54	1.61	1.32	-1.57
GO ; chymotrypsin activity ; 0004263	1.63	1.69	1.39	1.43	-1.57
GO ; G-protein coupled receptor activity ; 0004930	1.80	1.86	1.90	1.53	-1.57

Supplemental Table 4. Normalized enrichment values from GSEA analysis using sets of genes from Gene Ontology (GO) or the UniProt knowledgebase (KW). Red or green represents statistically significant up- or down- regulation, respectively.

GeneSet	low2d	low14d	high2d	high14d	g-dn
GO ; sodium ion transport ; 0006814	2.09	1.50	1.63	1.63	-1.55
GO ; potassium channel activity ; 0005267	1.57	1.62	1.69	1.51	-1.55
GO ; ion transport ; 0006811	1.58	1.35	1.46	1.17	-1.53
GO ; G-protein coupled receptor protein signaling pathway ; 0007186	1.51	1.60	1.57	1.28	-1.51
KW ; Transducer	1.49	1.56	1.51	1.28	-1.49
KW ; Sodium transport	2.01	1.37	1.52	1.57	-1.48
KW ; Ion transport	1.55	1.34	1.43	1.21	-1.47
KW ; Sodium	1.99	1.36	1.50	1.56	-1.44
KW ; Potassium channel	1.43	1.62	1.43	1.58	-1.43
KW ; Potassium transport	1.64	1.50	1.36	1.42	-1.39
GO ; potassium ion binding ; 0030955	1.69	1.46	1.39	1.43	-1.35
GO ; symporter activity ; 0015293	1.99	1.63	1.34	1.52	-1.34
KW ; Potassium	1.63	1.46	1.30	1.46	-1.32
KW ; mRNA splicing	-2.27	-2.12	-2.14	-1.46	1.92
GO ; immunoglobulin mediated immune response ; 0016064	-1.56	-1.58	-2.28	-1.80	1.90
GO ; RNA splicing ; 0008380	-2.23	-1.99	-2.09	-1.36	1.89
KW ; mRNA processing	-2.26	-2.03	-2.12	-1.55	1.82
GO ; positive regulation of immune response ; 0050778	-1.90	-1.62	-2.08	-1.50	1.75
GO ; mRNA processing ; 0006397	-2.08	-1.97	-2.06	-1.48	1.73
GO ; neural crest cell development ; 0014032	-1.76	-1.88	-1.63	-1.71	1.66
GO ; myeloid cell differentiation ; 0030099	-1.45	-1.93	-1.78	-1.94	1.63
GO ; ribonucleoside-diphosphate reductase activity ; 0004748	-1.87	-2.17	-1.84	-1.63	1.61
GO ; antigen processing and presentation of peptide or polysaccharide antigen via MHC class II ; 0002504	-2.44	-2.04	-2.49	-2.01	1.61

Supplemental Table 4. Normalized enrichment values from GSEA analysis using sets of genes from Gene Ontology (GO) or the UniProt knowledgebase (KW). Red or green represents statistically significant up- or down- regulation, respectively.

GeneSet	low2d	low14d	high2d	high14d	g-dn
GO ; MHC class II protein complex ; 0042613	-2.42	-2.04	-2.50	-1.93	1.58
GO ; common-partner SMAD protein phosphorylation ; 0007182	-1.85	-1.99	-2.18	-1.73	1.56
GO ; spliceosome ; 0005681	-2.03	-1.98	-2.09	-1.64	1.52
KW ; Chromatin regulator	-1.90	-1.58	-1.60	-1.39	1.44
GO ; chromatin modification ; 0016568	-1.77	-1.61	-1.71	-1.47	1.39
KW ; Spliceosome	-1.99	-2.11	-2.16	-1.65	1.37
GO ; regulation of GTPase activity ; 0043087	-1.58	-1.72	-1.68	-1.63	1.34
KW ; Chromosomal rearrangement	-1.47	-1.35	-1.38	-1.41	1.33
GO ; ubiquitin cycle ; 0006512	-1.69	-1.58	-1.65	-1.41	1.31
KW ; DNA damage	-1.42	-1.32	-1.37	-1.30	1.29
KW ; Proto-oncogene	-1.37	-1.36	-1.42	-1.33	1.29
KW ; DNA repair	-1.29	-1.32	-1.45	-1.25	1.27
GO ; response to DNA damage stimulus ; 0006974	-1.29	-1.32	-1.37	-1.41	1.22
KW ; Ubl conjugation pathway	-1.49	-1.57	-1.53	-1.42	1.19
KW ; Activator	-1.19	-1.48	-1.40	-1.28	1.11

Supplemental Table 5. Genes up-regulated in at least 1 rosiglitazone treatment group and changed (up or down) in mice containing a dominant negative PPAR gamma. Red or green represents statistically significant up- or down- regulation, respectively.

ProbeSet	low2d	low14d	high2d	high14d	gdn	gene	description
1420722_at	1.82	1.22	**2.25**	1.51	**0.16**	Elovl3	elongation of very long chain fatty acids (FEN1/Elo2, SUR4/Elo3, yeast)-like 3
1424451_at	**3.14**	**3.33**	**4.41**	**7.64**	**0.23**	Acaa1b	acetyl-Coenzyme A acyltransferase 1B
1416316_at	**3.29**	1.96	1.93	2.88	**0.33**	Slc27a2	solute carrier family 27 (fatty acid transporter), member 2
1451679_at	**2.03**	1.51	**2.12**	**2.09**	**0.41**	6530401D17Rik	RIKEN cDNA 6530401D17 gene
1418328_at	**2.37**	1.80	1.41	2.02	**0.42**	Cpt1b	carnitine palmitoyltransferase 1b, muscle
1428333_at	**2.71**	**1.82**	**3.01**	**2.83**	**0.42**	2900062L11Rik	RIKEN cDNA 2900062L11 gene
1436233_at	**2.25**	**2.17**	**2.44**	**4.58**	**0.43**	AI117581	expressed sequence AI117581
1449218_at	**2.20**	**2.13**	1.51	**2.64**	**0.46**	Cox8b	cytochrome c oxidase, subunit VIIIb
1449461_at	**3.51**	**2.75**	**3.97**	**6.88**	**0.48**	Rbp7	retinol binding protein 7, cellular
1460521_a_at	1.35	1.13	1.24	**1.72**	**0.50**	Obfc2a	oligonucleotide/oligosaccharide-binding fold containing 2A
1416023_at	1.47	**1.82**	1.21	**2.50**	**0.54**	Fabp3	fatty acid binding protein 3, muscle and heart
1448499_a_at	**1.69**	**1.61**	**1.71**	**2.34**	**0.60**	Ephx2	epoxide hydrolase 2, cytoplasmic
1453004_at	**1.48**	1.25	1.09	1.41	**0.64**	3110004L20Rik	RIKEN cDNA 3110004L20 gene
1448382_at	**1.77**	1.32	**1.54**	**1.85**	**0.66**	Ehhadh	enoyl-Coenzyme A, hydratase/3-hydroxyacyl Coenzyme A dehydrogenase
1454067_a_at	**1.57**	**1.56**	**1.71**	**1.93**	**0.66**	4931406C07Rik	RIKEN cDNA 4931406C07 gene
1431789_s_at	**1.40**	**1.41**	**1.51**	**1.57**	**0.68**	Tmed5	transmembrane emp24 protein transport domain containing 5

Supplemental Table 5. Genes up-regulated in at least 1 rosiglitazone treatment group and changed (up or down) in mice containing a dominant negative PPAR gamma. Red or green represents statistically significant up- or down- regulation, respectively.

ProbeSet	low2d	low14d	high2d	high14d	gdn	gene	description
1425216_at	1.21	1.19	**1.34**	1.19	**0.69**	Ffar2	free fatty acid receptor 2
1428435_at	1.16	1.18	**1.40**	**1.38**	**0.70**	Muc2	mucin 2
1453592_at	1.20	1.22	**1.42**	**1.44**	**0.71**	Lrrc39	leucine rich repeat containing 39
1417023_a_at	**1.71**	**1.64**	**1.86**	**1.90**	**0.71**	Fabp4	fatty acid binding protein 4, adipocyte
1424653_at	**1.28**	1.15	1.02	1.01	**0.72**	LOC669875	similar to Tetraspanin-15 (Tspan-15) (Transmembrane 4 superfamily member 15) (Tetraspan NET-7)
1432380_s_at	**1.31**	1.25	1.26	1.21	**0.72**	LOC665769	similar to gasdermin 1
1455279_at	1.22	**1.29**	1.17	1.21	**0.74**	Gm1060	gene model 1060, (NCBI)
1444063_at	1.24	1.10	**1.32**	**1.32**	**0.74**	5430435G22Rik	RIKEN cDNA 5430435G22 gene
1445802_at	1.22	**1.30**	**1.35**	1.26	**0.76**	AU017455	Expressed sequence AU017455
1415847_at	1.21	**1.31**	1.09	1.19	**0.77**	Ldhc	lactate dehydrogenase C
1439838_a_at	1.15	**1.23**	1.10	1.16	**0.78**	Tmie	transmembrane inner ear
1432749_at	1.11	**1.22**	1.07	1.04	**0.79**	Cryga	Crystallin, gamma A
1458260_at	**1.26**	1.03	1.11	1.14	**0.79**	Espn	Espin
1458377_at	**1.24**	1.19	1.05	1.11	**0.80**	Crsp7	cofactor required for Sp1 transcriptional activation, subunit 7
1420571_at	1.06	**1.20**	**1.24**	1.10	**0.80**	Prlpb	prolactin-like protein B
1453932_at	**1.23**	1.02	1.21	1.15	**0.80**	4931433A01Rik	RIKEN cDNA 4931433A01 gene

Supplemental Table 5. Genes up-regulated in at least 1 rosiglitazone treatment group and changed (up or down) in mice containing a dominant negative PPAR gamma. Red or green represents statistically significant up- or down- regulation, respectively.

ProbeSet	low2d	low14d	high2d	high14d	gdn	gene	description
1459974_x_at	**1.24**	1.18	1.19	1.07	**0.80**	Tbc1d9b	TBC1 domain family, member 9B
1454291_at	1.19	1.14	1.13	**1.25**	**0.80**	4933428P19Rik	RIKEN cDNA 4933428P19 gene
1446574_at	**1.37**	1.18	**1.30**	**1.27**	**0.80**	Ncor1	Nuclear receptor co-repressor 1
1453123_at	1.05	1.11	**1.25**	1.02	**0.81**	Sf3b2	splicing factor 3b, subunit 2
1435124_at	1.06	**1.22**	1.13	1.11	**0.81**	EG328644	predicted gene, EG328644
1433238_at	1.06	**1.21**	**1.22**	1.17	**0.81**	4930448E06Rik	RIKEN cDNA 4930448E06 gene
1425177_at	1.18	**1.27**	1.09	1.24	**0.81**	Shmt1	serine hydroxymethyl transferase 1 (soluble)
1443670_at	**1.24**	**1.24**	**1.27**	**1.27**	**0.81**	2010001J22Rik	RIKEN cDNA 2010001J22 gene
1423578_at	**1.23**	**1.26**	**1.25**	**1.37**	**0.81**	Col11a2	procollagen, type XI, alpha 2
1441211_at	1.14	**1.24**	**1.29**	**1.25**	**0.82**	Kcns2	K+ voltage-gated channel, subfamily S, 2
1426391_at	1.01	**1.23**	**1.25**	**1.30**	**0.83**	LOC545267	similar to ADP-ribosylation factor 1
1437646_at	1.18	**1.22**	**1.25**	1.19	**0.83**	LOC631806	similar to Goliath homolog precursor (Ring finger protein 130) (R-goliath)
1458027_at	1.07	1.18	**1.25**	1.13	**1.21**	Mrpl17	mitochondrial ribosomal protein L17
1442776_at	1.04	**1.28**	1.20	1.13	**1.24**	2310009E04Rik	RIKEN cDNA 2310009E04 gene
1437521_s_at	1.06	1.09	1.14	**1.26**	**1.25**	E230022H04Rik	RIKEN cDNA E230022H04 gene
1431004_at	**1.29**	1.05	1.17	1.04	**1.26**	Loxl2	lysyl oxidase-like 2

Supplemental Table 5. Genes up-regulated in at least 1 rosiglitazone treatment group and changed (up or down) in mice containing a dominant negative PPAR gamma. Red or green represents statistically significant up- or down- regulation, respectively.

ProbeSet	low2d	low14d	high2d	high14d	gdn	gene	description
1427830_at	1.08	1.06	1.20	**1.35**	**1.26**	Zfp260	zinc finger protein 260
1439028_at	1.19	1.21	**1.32**	**1.30**	**1.27**	Ufm1	ubiquitin-fold modifier 1
1447473_at	1.12	1.11	**1.37**	1.15	**1.30**	Anapc10	Transcribed locus
1440346_at	1.04	1.19	**1.29**	**1.27**	**1.33**	Jmjd3	Jumonji domain containing 3
1446968_at	1.12	1.10	**1.37**	1.27	**1.34**	Picalm	phosphatidylinositol binding clathrin assembly protein
1438842_at	1.05	1.15	**1.36**	1.33	**1.36**	Mtch2	mitochondrial carrier homolog 2 (C. elegans)
1420982_at	1.01	**1.26**	**1.27**	1.16	**1.39**	Rbm39	RNA binding motif protein 39
1418623_at	1.09	**1.35**	1.29	1.21	**1.43**	Rab2	RAB2, member RAS oncogene family
1436981_a_at	1.09	1.24	**1.63**	**1.78**	**1.57**	Ywhaz	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide
1438992_x_at	1.04	1.15	**1.45**	**1.57**	**1.58**	Atf4	activating transcription factor 4

Supplemental Table 6. Genes down-regulated in at least 1 rosiglitazone treatment group and changed (up or down) in mice containing a dominant negative PPAR gamma. Red or green represents statistically significant up- or down- regulation, respectively.

ProbeSet	low2d	low14d	high2d	high14d	gdn	gene	description
1448792_a_at	**0.62**	**0.38**	**0.32**	**0.39**	**3.97**	Cyp2f2	cytochrome P450, family 2, subfamily f, polypeptide 2
1440837_at	0.90	0.89	0.91	**0.70**	**1.64**	H2-Ob	histocompatibility 2, O region beta locus
1420650_at	0.77	**0.73**	0.82	0.96	**1.59**	Atbf1	AT motif binding factor 1
1429702_at	**0.62**	0.67	0.78	0.70	**1.56**	2900072G11Rik	RIKEN cDNA 2900072G11 gene
1450241_a_at	**0.78**	0.92	0.79	0.83	**1.50**	Evi2a	ecotropic viral integration site 2a
1418872_at	**0.71**	**0.64**	**0.70**	0.89	**1.45**	Abcb1b	ATP-binding cassette, sub-family B (MDR/TAP), member 1B
1419609_at	0.80	0.82	**0.74**	**0.72**	**1.45**	Ccr1	chemokine (C-C motif) receptor 1
1441370_at	**0.64**	0.72	0.82	0.95	**1.45**	Nfkbiz	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta
1456377_x_at	**0.69**	**0.68**	**0.58**	**0.75**	**1.44**	LOC632329	similar to epithelial protein lost in neoplasm
1455318_at	0.84	0.80	**0.72**	0.81	**1.41**	Timd4	T-cell immunoglobulin and mucin domain containing 4
1428447_at	0.77	**0.74**	0.90	0.81	**1.41**	Tmem14a	transmembrane protein 14A
1417045_at	0.83	**0.77**	**0.63**	**0.61**	**1.40**	Bid	BH3 interacting domain death agonist
1438427_at	0.82	**0.72**	**0.77**	**0.73**	**1.39**	4932442K08Rik	RIKEN cDNA 4932442K08 gene
1451335_at	**0.68**	**0.68**	**0.61**	0.75	**1.38**	Plac8	placenta-specific 8
1438592_at	0.87	0.97	**0.81**	0.83	**1.38**	Nek1	NIMA (never in mitosis gene a)-related expressed kinase 1
1435504_at	0.83	**0.72**	0.89	0.86	**1.37**	Rsnl2	Transcribed locus

Supplemental Table 6. Genes down-regulated in at least 1 rosiglitazone treatment group and changed (up or down) in mice containing a dominant negative PPAR gamma. Red or green represents statistically significant up- or down- regulation, respectively.

ProbeSet	**low2d**	**low14d**	**high2d**	**high14d**	**gdn**	**gene**	**description**
1438750_at	**0.73**	0.87	0.84	0.79	**1.36**	Atrx	Alpha thalassemia/mental retardation syndrome X-linked homolog (human)
1442576_at	**0.79**	0.84	0.85	0.93	**1.36**	Creb5	CAMP responsive element binding protein 5
1427183_at	**0.72**	**0.65**	**0.71**	0.89	**1.33**	Efemp1	epidermal growth factor-containing fibulin-like extracellular matrix protein 1
1457445_at	**0.78**	0.95	0.99	0.89	**1.33**	Trps1	trichorhinophalangeal syndrome I (human)
1460465_at	**0.74**	**0.73**	0.80	0.95	**1.32**	A930038C07Rik	RIKEN cDNA A930038C07 gene
1430038_at	0.90	**0.79**	**0.80**	**0.77**	**1.32**	Gphn	gephyrin
1451716_at	0.87	**0.80**	**0.80**	0.84	**1.32**	Mafb	v-maf musculoaponeurotic fibrosarcoma oncogene family, protein B (avian)
1416296_at	0.89	**0.79**	**0.73**	0.91	**1.32**	Il2rg	interleukin 2 receptor, gamma chain
1437414_at	**0.76**	**0.71**	0.84	0.79	**1.31**	Zfp217	zinc finger protein 217
1422744_at	**0.77**	**0.74**	0.87	**0.78**	**1.31**	Phka1	phosphorylase kinase alpha 1
1437410_at	**0.68**	**0.75**	0.82	0.89	**1.30**	Aldh2	aldehyde dehydrogenase 2, mitochondrial
1424965_at	**0.68**	**0.71**	**0.61**	**0.53**	**1.29**	Lpxn	leupaxin
1455224_at	**0.70**	**0.59**	**0.72**	**0.68**	**1.28**	Angptl1	angiopoietin-like 1
1434401_at	**0.79**	**0.80**	0.85	0.91	**1.25**	Zcchc2	zinc finger, CCHC domain containing 2
1431751_a_at	0.99	0.84	**0.82**	0.84	**1.25**	Mpped2	metallophosphoesterase domain containing 2
1436312_at	0.95	0.84	**0.79**	**0.79**	**1.24**	Ikzf1	IKAROS family zinc finger 1

Supplemental Table 6. Genes down-regulated in at least 1 rosiglitazone treatment group and changed (up or down) in mice containing a dominant negative PPAR gamma. Red or green represents statistically significant up- or down- regulation, respectively.

ProbeSet	low2d	low14d	high2d	high14d	gdn	gene	description
1460391_at	0.95	**0.83**	0.86	**0.78**	**1.24**	Gtpbp9	GTP-binding protein 9 (putative)
1446834_at	0.88	0.98	**0.83**	**0.74**	**1.24**	Ctsc	Cathepsin C
1450629_at	**0.82**	0.84	**0.78**	**0.81**	**1.19**	Lima1	LIM domain and actin binding 1
1421646_a_at	0.97	0.88	**0.86**	**0.82**	**0.86**	Pias3	protein inhibitor of activated STAT 3
1419617_at	0.94	0.94	**0.83**	0.85	**0.84**	Kcnn1	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 1
1448662_at	0.87	0.90	**0.82**	0.81	**0.83**	Fzd6	frizzled homolog 6 (Drosophila)
1431214_at	0.85	**0.68**	**0.66**	**0.65**	**0.82**	1300007C21Rik	RIKEN cDNA 1300007C21 gene
1426710_at	0.90	**0.79**	**0.59**	**0.63**	**0.82**	Calm3	calmodulin 3
1416493_at	0.90	**0.82**	**0.66**	**0.72**	**0.82**	Ddost	dolichyl-di-phosphooligosaccharide-protein glycotransferase
1452581_at	0.92	0.84	**0.77**	0.82	**0.82**	2610304G08Rik	RIKEN cDNA 2610304G08 gene
1422329_a_at	0.98	0.87	**0.78**	**0.76**	**0.82**	Ntrk3	neurotrophic tyrosine kinase, receptor, type 3
1460413_s_at	0.98	**0.84**	**0.84**	**0.83**	**0.82**	Zdhhc1	zinc finger, DHHC domain containing 1
1435560_at	0.93	**0.77**	**0.74**	**0.72**	**0.81**	LOC671163	similar to integrin alpha-L precursor (Leukocyte adhesion glycoprotein LFA-1 alpha chain) (LFA-1A) (Leukocyte function-associated molecule 1 alpha chain) (Lymphocyte antigen Ly-15) (CD11a antigen)
1421042_at	0.93	**0.81**	**0.67**	**0.78**	**0.81**	Arhgef2	rho/rac guanine nucleotide exchange factor (GEF) 2
1452376_at	0.98	0.90	**0.74**	**0.67**	**0.81**	Zfp444	zinc finger protein 444
1416497_at	0.83	**0.75**	**0.66**	**0.69**	**0.80**	Pdia4	protein disulfide isomerase associated 4

Supplemental Table 6. Genes down-regulated in at least 1 rosiglitazone treatment group and changed (up or down) in mice containing a dominant negative PPAR gamma. Red or green represents statistically significant up- or down- regulation, respectively.

ProbeSet	low2d	low14d	high2d	high14d	gdn	gene	description
1450409_a_at	0.97	**0.81**	**0.75**	**0.69**	**0.80**	4930570C03Rik	RIKEN cDNA 4930570C03 gene
1426738_at	0.99	0.86	**0.74**	**0.72**	**0.80**	Dgkz	diacylglycerol kinase zeta
1460305_at	0.97	0.89	**0.79**	**0.72**	**0.80**	Itga3	integrin alpha 3
1421026_at	0.81	**0.73**	**0.57**	**0.63**	**0.79**	Gna12	guanine nucleotide binding protein, alpha 12
1450378_at	0.87	**0.77**	**0.61**	**0.66**	**0.79**	Tapbp	TAP binding protein
1416322_at	0.87	**0.75**	**0.66**	**0.64**	**0.79**	Prelp	proline arginine-rich end leucine-rich repeat
1453960_a_at	0.88	**0.78**	**0.63**	**0.64**	**0.79**	Capzb	capping protein (actin filament) muscle Z-line, beta
1421044_at	0.85	**0.80**	**0.72**	**0.57**	**0.79**	Mrc2	mannose receptor, C type 2
1417949_at	0.84	**0.78**	**0.73**	**0.65**	**0.79**	Ilf2	interleukin enhancer binding factor 2
1426379_at	0.97	0.84	**0.76**	0.82	**0.79**	Eif4b	eukaryotic translation initiation factor 4B
1452024_a_at	0.99	0.89	**0.73**	0.80	**0.79**	Ldb1	LIM domain binding 1
1428850_x_at	0.89	**0.70**	**0.56**	**0.63**	**0.78**	Cd99	CD99 antigen
1416038_at	0.87	**0.72**	**0.65**	**0.60**	**0.78**	AL033314	expressed sequence AL033314
1450097_s_at	0.91	**0.76**	**0.66**	**0.67**	**0.78**	Gna12	guanine nucleotide binding protein, alpha 12
1450325_at	0.92	**0.78**	**0.70**	**0.73**	**0.78**	Angpt4	angiopoietin 4
1450038_s_at	**0.79**	**0.79**	0.81	0.80	**0.78**	Usp9x	ubiquitin specific peptidase 9, X chromosome

Supplemental Table 6. Genes down-regulated in at least 1 rosiglitazone treatment group and changed (up or down) in mice containing a dominant negative PPAR gamma. Red or green represents statistically significant up- or down- regulation, respectively.

ProbeSet	**low2d**	**low14d**	**high2d**	**high14d**	**gdn**	**gene**	**description**
1421276_a_at	0.85	0.86	**0.75**	**0.74**	**0.78**	Dst	dystonin
1417015_at	0.88	0.92	**0.71**	**0.71**	**0.78**	Rassf3	Ras association (RalGDS/AF-6) domain family 3
1418082_at	0.96	0.84	0.91	**0.67**	**0.78**	Nmt1	N-myristoyltransferase 1
1434370_s_at	0.99	**0.82**	**0.79**	**0.81**	**0.78**	Faf1	Fas-associated factor 1
1421860_at	0.88	**0.74**	**0.65**	**0.63**	**0.77**	Clstn1	calsyntenin 1
1453622_s_at	0.83	**0.77**	**0.76**	**0.74**	**0.77**	Mllt3	myeloid/lymphoid or mixed lineage-leukemia translocation to 3 homolog (Drosophila)
1422622_at	0.93	0.77	**0.77**	0.82	**0.77**	Nos3	nitric oxide synthase 3, endothelial cell
1427797_s_at	0.86	**0.73**	**0.68**	**0.65**	**0.76**	EG622147	hypothetical protein LOC670510
1416732_at	0.79	0.87	0.79	**0.69**	**0.76**	Top2b	topoisomerase (DNA) II beta
1451678_at	0.99	0.95	**0.77**	0.85	**0.76**	Narf	nuclear prelamin A recognition factor
1449018_at	0.80	**0.67**	**0.46**	**0.54**	**0.75**	Pfn1	profilin 1
1423554_at	0.90	**0.72**	**0.63**	**0.66**	**0.75**	Ggcx	gamma-glutamyl carboxylase
1418075_at	0.96	0.78	**0.60**	**0.65**	**0.75**	St6galnac4	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 4
1419099_x_at	0.99	0.85	**0.66**	**0.68**	**0.75**	Stom	stomatin
1433744_at	0.83	0.88	0.93	**0.76**	**0.75**	Lrtm2	leucine-rich repeats and transmembrane domains 2
1422044_at	0.87	0.92	**0.77**	0.84	**0.75**	Ndst1	N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 1

Supplemental Table 6. Genes down-regulated in at least 1 rosiglitazone treatment group and changed (up or down) in mice containing a dominant negative PPAR gamma. Red or green represents statistically significant up- or down- regulation, respectively.

ProbeSet	low2d	low14d	high2d	high14d	gdn	gene	description
1421721_a_at	0.93	0.97	**0.75**	0.83	**0.75**	Arnt	aryl hydrocarbon receptor nuclear translocator
1432344_a_at	0.88	**0.67**	**0.59**	**0.61**	**0.74**	Aplp2	amyloid beta (A4) precursor-like protein 2
1451734_a_at	0.92	0.78	**0.67**	0.77	**0.74**	Dbn1	drebrin 1
1451737_at	0.89	0.83	**0.74**	**0.68**	**0.74**	Pik3r1	phosphatidylinositol 3-kinase, regulatory subunit, polypeptide 1 (p85 alpha)
1432211_a_at	0.91	0.81	**0.71**	**0.74**	**0.74**	Fbxo9	f-box protein 9
1425344_at	0.89	**0.76**	0.78	0.75	**0.74**	Narf	nuclear prelamin A recognition factor
1426458_at	0.83	**0.72**	0.85	0.78	**0.74**	Slmap	sarcolemma associated protein
1422845_at	0.81	**0.74**	**0.65**	**0.69**	**0.73**	Canx	calnexin
1453931_at	0.93	**0.80**	**0.76**	**0.74**	**0.73**	Col14a1	procollagen, type XIV, alpha 1
1443805_at	0.80	**0.71**	**0.59**	**0.61**	**0.72**	Dact3	dapper homolog 3, antagonist of beta-catenin (xenopus)
1430514_a_at	0.88	**0.71**	**0.53**	**0.63**	**0.72**	Cd99	CD99 antigen
1421245_at	0.95	0.87	**0.61**	**0.70**	**0.71**	Sost	sclerostin
1422987_at	0.94	**0.71**	**0.77**	**0.71**	**0.68**	Ntn1	netrin 1
1425285_a_at	0.91	0.85	**0.75**	**0.78**	**0.67**	Rab27a	RAB27A, member RAS oncogene family
1421431_at	0.89	0.74	**0.61**	**0.55**	**0.55**	Ptrf	polymerase I and transcript release factor

Supplemental Table 7. Number of genes that were differentially expressed in both rosiglitazone-treated and G-DN mice. NS = non-significant change.

Up with rosiglitazone (# significant changes)	total genes	gdn-down	gdn-up	gdn-ns
1	410	44	14	352
2	180	24	5	151
3	75	16	0	59
4	33	10	0	23
Down with rosiglitazone (# significant changes)	**total genes**	**gdn-down**	**gdn-up**	**gdn-ns**
1	1040	60	35	945
2	588	45	22	521
3	255	30	12	213
4	32	0	4	28

Supplemental Table 8. G-DN specific changes in expression of genes involved in oxidoreductase actvity or transcriptional regulation. Red or green represents statistically significant up- or down- regulation, respectively.

ProbeSetID	low2d	low14d	high2d	high14d	g-dn	Gene	GeneID	Description
Oxidoreductase Activity; GO:0016491								
1417651_at	0.94	0.88	1.07	1.04	0.57	Cyp2c29	13095	cytochrome P450, family 2, subfamily c, polypeptide 29
1424618_at	1.07	1.09	1.02	1.02	0.64	Hpd	15445	4-hydroxyphenylpyruvic acid dioxygenase
1441271_at	1.14	1.07	0.92	0.97	0.66	Idh3b	170718	Isocitrate dehydrogenase 3 (NAD+) beta
1418506_a_at	1.16	1.00	0.94	0.93	0.69	Prdx2	21672	peroxiredoxin 2
1450715_at	1.06	0.93	1.08	1.19	0.69	Cyp1a2	13077	cytochrome P450, family 1, subfamily a, polypeptide 2
1451386_at	1.09	0.90	0.82	0.86	0.72	Blvrb	233016	biliverdin reductase B (flavin reductase (NADPH))
1448800_at	1.24	1.12	1.02	1.01	0.72	Rtn4ip1	170728	reticulon 4 interacting protein 1
1429972_s_at	1.24	0.99	0.92	0.95	0.73	Txnrd2	26462	thioredoxin reductase 2
1418113_at	0.96	0.95	0.90	0.90	0.75	Cyp2d10	13101	cytochrome P450, family 2, subfamily d, polypeptide 10

Supplemental Table 8. G-DN specific changes in expression of genes involved in oxidoreductase actvity or transcriptional regulation. Red or green represents statistically significant up- or down- regulation, respectively.

ProbeSetID	**low2d**	**low14d**	**high2d**	**high14d**	**g-dn**	**Gene**	**GeneID**	**Description**
Regulation of transcription, DNA-dependent; GO:0006355								
1419913_at	0.87	1.00	1.09	1.23	1.83	Strap	20901	Serine/threonine kinase receptor associated protein
1460407_at	1.08	0.87	0.91	0.90	1.75	Spib	272382	Spi-B transcription factor (Spi-1/PU.1 related)
1446148_x_at	0.83	1.01	0.98	1.10	1.59	C79248	96982	expressed sequence C79248
1421564_at	1.24	0.88	0.80	0.75	1.50	Serpina3c	16625	serine (or cysteine) peptidase inhibitor, clade A, member 3C
1444229_at	0.84	0.93	0.99	1.05	1.50	Nr2f2	11819	nuclear receptor subfamily 2, group F, member 2
1449661_at	0.91	1.05	1.04	0.97	1.46	Suz12	52615	Suppressor of zeste 12 homolog (Drosophila)
1456916_at	0.94	0.95	1.05	0.99	1.42	Nsd1	18193	Nuclear receptor-binding SET-domain protein 1
1433512_at	0.89	0.91	1.07	1.28	1.40	Fli1	14247	Friend leukemia integration 1
1435337_at	0.86	0.98	1.04	1.15	1.36	Tshz3	243931	teashirt zinc finger family member 3
1420615_at	0.91	0.89	0.95	1.07	1.33	Ash2l	23808	ash2 (absent, small, or homeotic)-like (Drosophila)
1453267_at	0.84	0.95	1.04	1.05	1.31	Atbf1	11906	AT motif binding factor 1
1460491_at	0.89	0.86	0.99	0.88	1.27	Invs	16348	inversin
1436392_s_at	0.96	0.99	1.09	1.09	1.27	Tcfap2c	21420	transcription factor AP-2, gamma
1446405_at	0.95	1.09	1.17	1.11	1.21	Myst3	244349	MYST histone acetyltransferase (monocytic leukemia) 3