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

Running title: Diabetic complications in db/db mice

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Supplementary Figure 1. Effects of pioglitazone on body weight. Representative images of the db/db mouse following 11wk of pioglitazone treatment (A) and untreated db/db mouse (B)
Supplementary Figure 2. Effects of pioglitazone on GHb level in plasma. Following 11 weeks of pioglitazone treatment GHb (mmol/mol) was assessed. * p<0.05; ** p<0.01; *** p<0.001. In all panels, n = 6.
Supplementary Figure 3. Effects of pioglitazone on kidney function. Following 11 weeks of pioglitazone treatment, 24-hour urinary albumin excretion (A), albuminuria, based on albumin/creatinine ratios (ACRs) (B), and mesangial matrix accumulation (C) were assessed. *** p<0.001. In all panels, n = 6.
Supplementary Figure 4. Effects of pioglitazone on diabetic glomerulopathy. Changes in glomerular matrix accumulation using a periodic acid Schiff (PAS) stain (A) for four animal groups (A1: \( db/+ \), A2: \( db/+ \) PIO, A3: \( db/db \), and A4: \( db/db \) PIO) and assessments of glomerular area (B) and glomerular PAS-positive area (C). ** p<0.01; *** p<0.001. In all groups, n = 6.
**Supplementary Table 1.** List of primers used for validation of gene expression data by RT-qPCR. Primers were selected using PrimerBank (http://pga.mgh.harvard.edu/primerbank/) and purchased from Integrated DNA Technologies.

| GeneID | Primer | Forward | Reverse | Fragment Size (bp) |
|--------|--------|---------|---------|-------------------|
| 93726  | Ear11  | TGGAGCAACTTGAGTCTCGAC | CCGGGATAGGTCTGTATAGA | 130 |
| 19017  | Ppargc1a | CTGTATGGAGTGACATAGTGTGC | GAAAGCTGTCTGTATCCAGTCATT | 120 |
| 216343 | Tph2   | FATGGAGCGAGGTTACCTTCGT | GTCTGAAAGGTTGGATAGG | 126 |
| 22227  | Ucp1   | AGGCTTCCAGTACCATTAGGT | CTGAGTGAGGCAAGCTGATTT | 133 |
**Supplementary Table 2. Validation of microarray data using RT-PCR.** Table indicates the fold change (FC) of DEGs, against Tyrosine 3-Monoxygenase/Tryptophan 5-Monoxygenase Activation (*Ywhaz*) gene as the endogenous control, from microarray that were selected for validation by RT-qPCR. *, p<0.05, ***, p<0.001

| 16 wk DEG                                                                 | Symbol | Gene ID | Array (FC) *db/db vs. db/db PIO* | qPCR (FC) *db/db vs. db/db PIO* |
|--------------------------------------------------------------------------|--------|---------|---------------------------------|---------------------------------|
| uncoupling protein 1 (mitochondrial, proton carrier)                     | *UCP1* | 22227   | 8.75                            | 3.80***                         |
| acetyl-Coenzyme A acyltransferase 1B                                     | *Acaa1b* | 235674 | 2.43                            | 1.11                            |
| cell death-inducing DNA fragmentation factor, alpha subunit-like effector A | *Cidea* | 12683   | 1.95                            | 2.51*                           |
| peroxisome proliferative activated receptor, gamma, coactivator 1 alpha   | *Ppargc1a* | 19017   | 1.23                            | 1.05                            |
**Supplementary Table 3. The overlap summary of the four DRG DEG sets in Figure 5A.** The numbers in each cell follow the "A (B | C)" format, where A is the number of common DEGs, B is the number of common DEGs with the same direction of change, and C is the number of DEGs with opposite direction of change.

| DEG Sets                  | # DEGs | db/+ vs db/+ PIO | db/+ vs db/db | db/+ PIO vs db/db PIO | db/db vs db/db PIO |
|---------------------------|--------|------------------|---------------|-----------------------|-------------------|
| db/+ vs db/+ PIO          | 24     | 24 (24|0)          | 12 (12|0)       | 6 (4|2)                | 4 (4|0)           |
| db/+ vs db/db             | 2082   | 12 (12|0)         | 2082 (2082|0)  | 804 (758|46)           | 455 (116|339)      |
| db/+ PIO vs db/db PIO     | 2478   | 6 (4|2)          | 804 (758|46)   | 2478 (2478|0)         | 802 (784|18)       |
| db/db vs db/db PIO        | 1811   | 4 (4|0)          | 455 (116|339)  | 802 (784|18)           | 1811 (1811|0)     |
Supplementary Table 4. The 20 most up-regulated genes and 20 most down-regulated genes that are dysregulated by diabetes and reversed by pioglitazone treatment in DRG. FC: fold-change; FDR: false discovery rate. Color indicates the up (red) or down (blue) regulation in the second group (eg. *db/db* in the *db/+* vs *db/db* comparison)

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

| GeneID     | Symbol  | Description                                                      | db/+ vs db/db | db/db vs db/db PIO |
|------------|---------|------------------------------------------------------------------|---------------|--------------------|
| 100503092  | Gm19550 | hypothetical LOC100503092                                        | -1.30         | 1.1E-03            |
| 69358      | Lrrc51  | leucine rich repeat containing 51                                | -1.30         | 2.8E-03            |
| 170458     | Gpha2   | glycoprotein hormone alpha 2                                     | -1.31         | 1.9E-02            |
| 66120      | Fkbp11  | FK506 binding protein 11                                          | -1.32         | 6.0E-03            |
| 212390     | Khi32   | kelch-like 32 (Drosophila)                                       | -1.34         | 1.8E-03            |
| 237625     | Pla2g3  | phospholipase A2, group III                                      | -1.35         | 2.2E-03            |
| 67119      | Ccdc159 | coiled-coil domain containing 159                                | -1.38         | 2.3E-03            |
| 75579      | 2310034G01Rik | RIKEN cDNA 2310034G01 gene                    | -1.39         | 1.6E-02            |
| 104362     | Meig1   | meiosis expressed gene 1                                          | -1.43         | 4.0E-03            |
| 235330     | Ttc12   | tetratricopeptide repeat domain 12                               | -1.43         | 2.3E-04            |
| 27274      | Zfp354b | zinc finger protein 354B                                          | -1.45         | 1.6E-02            |
| 28240      | Trpm2   | transient receptor potential cation channel, subfamily M, member 2| -1.45         | 1.6E-03            |
| 140743     | Rem2    | rad and gem related GTP binding protein 2                         | -1.48         | 3.9E-05            |
| 232146     | Eva1a   | family with sequence similarity 176, member A                    | -1.50         | 3.4E-03            |

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

| GeneID   | Symbol       | Description                                                                 | db/+ vs db/db | db/db vs db/db PIO |
|----------|--------------|------------------------------------------------------------------------------|---------------|-------------------|
| 71760    | Agxt2l1      | alanine-glyoxylate aminotransferase 2-like 1                                 | 3.80          | 2.9E-05           |
| 12491    | Cd36         | CD36 antigen                                                                 | 2.30          | 2.4E-03           |
| 11450    | Adipoq       | adiponectin, C1Q and collagen domain containing                               | 2.21          | 3.8E-02           |
| 16846    | Lep          | leptin                                                                       | 1.88          | 2.6E-02           |
| 71406    | S430416009Rik| RIKEN cDNA S430416009 gene                                                    | 1.87          | 6.0E-04           |
| 70358    | Steap1       | six transmembrane epithelial antigen of the prostate 1                       | 1.60          | 5.6E-03           |
| 230379   | Acer2        | alkaline ceramidase 2                                                        | 1.47          | 1.6E-02           |
| 54153    | Rasa4        | RAS p21 protein activator 4                                                  | 1.38          | 2.7E-04           |
| 207798   | Gramd1c      | GRAM domain containing 1C                                                     | 1.36          | 2.8E-03           |
| 68453    | Gpihbp1      | GPI-anchored HDL-binding protein 1                                            | 1.36          | 3.9E-02           |
| 75180    | 4930538K18Rik| RIKEN cDNA 4930538K18 gene                                                    | 1.34          | 3.0E-02           |
| 237246   | BC022960     | cDNA sequence BC022960                                                       | 1.31          | 1.2E-02           |
| 78751    | Zc3h6        | zinc finger CCCH type containing 6                                            | 1.30          | 4.1E-02           |
| 16890    | Lipe         | lipase, hormone sensitive                                                    | 1.30          | 4.8E-02           |
| 56448    | Cyp2d22      | cytochrome P450, family 2, subfamily d, polypeptide 22                        | 1.30          | 3.7E-03           |
| 53608    | Map3k6       | mitogen-activated protein kinase kinase 6                                    | 1.29          | 7.9E-03           |
| 20514    | Slc1a5       | solute carrier family 1 (neutral amino acid transporter), member 5           | 1.29          | 9.7E-03           |
| 269630   | 5031425E22Rik| RIKEN cDNA 5031425E22 gene                                                    | 1.26          | 3.4E-02           |
| 73001    | 2900055J20Rik| RIKEN cDNA 2900055J20 gene                                                    | 1.25          | 2.4E-03           |
| 216233   | Soc2         | suppressor of cytokine signaling 2                                           | 1.25          | 2.5E-03           |
| 230235   | Frrs1l       | RIKEN cDNA 6430704M03 gene                                                   | -1.22         | 1.3E-02           |
| 16416    | Itgb3        | integrin beta 3                                                              | -1.22         | 2.2E-02           |
| 378462   | Morn2        | MORN repeat containing 2                                                     | -1.22         | 1.0E-03           |
| 12168    | Bmpr2        | bone morphogenic protein receptor, type II (serine/threonine kinase)         | -1.22         | 2.0E-02           |
| 12443    | Ccnd1        | cyclin D1                                                                    | -1.22         | 9.5E-04           |
| 234700   | Nrn1l        | neuritin 1-like                                                              | -1.23         | 4.3E-03           |

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## SUPPLEMENTARY DATA

| GeneID | Symbol | Description                                                                 | db/+ vs db/db |       |       | db/db vs db/db |       |
|--------|--------|------------------------------------------------------------------------------|---------------|-------|-------|----------------|-------|
| 22027  | Hsp90b1| heat shock protein 90, beta (Grp94), member 1                               | -1.23         | 9.4E-04 | -1.17 | 3.1E-03        |       |
| 70356  | St13   | suppression of tumorigenicity 13                                            | -1.24         | 8.9E-03 | -1.24 | 1.4E-02        |       |
| 15505  | Hsp1   | heat shock 105kDa/110kDa protein 1                                           | -1.24         | 4.9E-04 | -1.21 | 2.6E-03        |       |
| 12140  | Fabp7  | fatty acid binding protein 7, brain                                          | -1.24         | 3.8E-03 | -1.42 | 1.3E-02        |       |
| 216166 | Plk5   | polo-like kinase 5 (Drosophila)                                             | -1.29         | 1.2E-02 | -1.31 | 1.4E-02        |       |
| 106869 | Tnfaip8| tumor necrosis factor, alpha-induced protein 8                              | -1.34         | 6.3E-03 | -1.40 | 1.8E-02        |       |
| 16840  | Lect1  | leukocyte cell derived chemotaxin 1                                         | -1.34         | 2.2E-04 | -1.13 | 2.8E-02        |       |
| 384061 | Fndc5  | fibronectin type III domain containing 5                                    | -1.39         | 2.5E-04 | -1.12 | 4.3E-02        |       |
| 18451  | P4ha1  | procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), alpha 1 polypeptide | -1.46         | 9.1E-04 | -1.30 | 2.8E-02        |       |
| 170813 | Ms4a3  | membrane-spanning 4-domains, subfamily A, member 3                          | -1.47         | 2.7E-03 | -1.46 | 8.4E-03        |       |
| 12406  | Serpinh1| serine (or cysteine) peptidase inhibitor, clade H, member 1                 | -1.53         | 8.4E-03 | -1.88 | 2.0E-03        |       |
| 71111  | Gpr39  | G protein-coupled receptor 39                                               | -1.57         | 6.9E-03 | -1.37 | 5.0E-03        |       |
| 20290  | Ccl1   | chemokine (C-C motif) ligand 1                                               | -1.61         | 9.0E-04 | -1.26 | 4.3E-02        |       |
| 72585  | Lypd1  | Ly6/Plaur domain containing 1                                               | -1.62         | 1.5E-03 | -1.32 | 2.9E-03        |       |
**Supplementary Table 6.** The 20 most up-regulated genes and 20 most down-regulated genes that are dysregulated only by diabetes (db/+ vs db/db) and not by pioglitazone treatment in DRG. FC: fold-change; FDR: false discovery rate.

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

| GeneID | Symbol | Description                                                                 | FC  | FDR       |
|--------|--------|-----------------------------------------------------------------------------|-----|-----------|
| 58807  | Slco1c1| solute carrier organic anion transporter family, member 1c1                | -1.72| 1.2E-04  |
| 107146 | Glyat  | glycine-N-acyltransferase                                                   | -1.78| 1.3E-02  |
| 210463 | Slc22a22| cDNA sequence BC026439                                                      | -1.79| 5.1E-04  |
| 246048 | Chodl  | chondrolectin                                                               | -1.80| 3.6E-03  |
| 97114  | Hist2h3c2| histone cluster 2, H3c2, pseudogene                                          | -1.80| 2.9E-05  |
| 229550 | 9130204L05Rik | Riken cDNA 9130204L05 gene                                                   | -1.84| 2.0E-02  |
| 16019  | Ighm   | immunoglobulin heavy chain 6 (heavy chain of IgM)                           | -1.84| 5.0E-03  |
| 18857  | Pmp2   | peripheral myelin protein 2                                                 | -1.97| 3.5E-03  |
| 74748  | Slamf8 | SLAM family member 8                                                        | -1.97| 3.2E-02  |
| 57262  | Retnla | resistin like alpha                                                         | -2.14| 2.0E-02  |
| 66198  | Them5  | thioesterase superfamily member 5                                           | -2.16| 1.2E-04  |
| 109254 | Adtrp  | RIKEN cDNA 9530008L14 gene                                                  | -2.45| 5.5E-04  |
**Supplementary Table 7.** The 20 most up-regulated genes and 20 most down-regulated genes that are dysregulated only by pioglitazone treatment (*db/db* vs *db/db* PIO) and not by diabetes (*db/+* vs *db/db*) in DRG. FC: fold-change; FDR: false discovery rate.

| GeneID  | Symbol | Description                                                                 | FC    | FDR     |
|---------|--------|------------------------------------------------------------------------------|-------|---------|
| 22227   | Ucp1   | uncoupling protein 1 (mitochondrial, proton carrier)                         | 8.75  | 4.3E-03 |
| 14311   | Cidec  | cell death-inducing DFFA-like effector c                                    | 6.86  | 1.3E-03 |
| 11770   | Fabp4  | fatty acid binding protein 4, adipocyte                                     | 5.10  | 5.6E-04 |
| 93726   | Ear11  | eosinophil-associated, ribonuclease A family, member 11                     | 4.85  | 6.6E-04 |
| 13106   | Cyp2e1 | cytochrome P450, family 2, subfamily e, polypeptide 1                        | 4.64  | 6.5E-03 |
| 24108   | Ubd    | ubiquitin D                                                                  | 4.03  | 3.4E-03 |
| 63954   | Rbp7   | retinol binding protein 7, cellular                                          | 2.96  | 1.9E-04 |
| 246747  | Adig   | adipogenin                                                                   | 2.95  | 1.2E-03 |
| 16956   | Lpl    | lipoprotein lipase                                                           | 2.91  | 3.9E-03 |
| 57264   | Retn   | resistin                                                                     | 2.49  | 6.8E-03 |
| 235674  | Aca1b  | acetyl-Coenzyme A acyltransferase 1B                                         | 2.43  | 6.2E-03 |
| 13850   | Ephx2  | epoxide hydrolase 2, cytoplasmian                                            | 2.11  | 3.4E-03 |
| 71939   | Apol6  | apolipoprotein L 6                                                           | 2.07  | 4.1E-02 |
| 58805   | Mlxipl | MLX interacting protein-like                                                 | 1.98  | 4.0E-02 |
| 12683   | Cidea  | cell death-inducing DNA fragmentation factor, alpha subunit-like effector A | 1.95  | 9.5E-03 |
| 18113   | Nnmt   | nicotinamide N-methyltransferase                                             | 1.91  | 4.1E-02 |
| 232493  | Gys2   | glycogen synthase 2                                                          | 1.85  | 2.6E-02 |
| 13120   | Cyp4b1 | cytochrome P450, family 4, subfamily b, polypeptide 1                        | 1.84  | 5.4E-03 |
| 240239  | Gpr151 | G protein-coupled receptor 151                                              | 1.79  | 4.8E-02 |
| 22690   | Zfp28  | zinc finger protein 28                                                        | 1.67  | 6.7E-04 |
| 11537   | Cfd    | complement factor D (adipsin)                                                | -1.86 | 4.8E-02 |
| 60361   | Ms4a4b | membrane-spanning 4-domains, subfamily A, member 4B                          | -1.91 | 6.4E-03 |
| 15985   | Cd79b  | CD79B antigen                                                                | -1.92 | 5.4E-03 |
| 14960   | H2-Aa  | histocompatibility 2, class II antigen A, alpha                              | -1.93 | 2.6E-03 |
| 227929  | Cytip  | cytohesin 1 interacting protein                                              | -1.93 | 2.6E-03 |
| 20345   | Selplg | selectin, platelet (p-selectin) ligand                                       | -1.94 | 1.4E-02 |
| 100504404 | H2-Ea-ps | h-2 class II histocompatibility antigen, E-K alpha chain-like                  | -2.04 | 2.6E-03 |
| 21973   | Top2a  | topoisomerase (DNA) II alpha                                                  | -2.08 | 8.0E-03 |
## SUPPLEMENTARY DATA

| GeneID  | Symbol | Description                                | FC   | FDR   |
|---------|--------|--------------------------------------------|------|-------|
| 50706   | Postn  | periostin, osteoblast specific factor       | -2.09| 5.0E-04|
| 14969   | H2-Eb1 | histocompatibility 2, class II antigen E beta | -2.11| 2.6E-03|
| 11687   | Alox15 | arachidonate 15-lipoxygenase                | -2.18| 3.4E-02|
| 16071   | IgkC   | immunoglobulin kappa chain, constant region | -2.28| 2.1E-02|
| 23833   | Cd52   | CD52 antigen                                | -2.43| 1.3E-03|
| 53856   | Prg3   | proteoglycan 3                              | -2.46| 3.3E-02|
| 64380   | Ms4a4c | membrane-spanning 4-domains, subfamily A, member 4C | -2.64| 1.3E-03|
| 231507  | Plac8  | placenta-specific 8                         | -2.66| 1.8E-03|
| 13861   | Epx    | eosinophil peroxidase                       | -2.69| 3.0E-02|
| 20343   | Sell   | selectin, lymphocyte                       | -2.74| 5.5E-03|
| 328563  | Apol11b| apolipoprotein L 11b                        | -2.83| 8.5E-03|
| 20558   | Slfn4  | schlafen 4                                  | -3.36| 7.1E-04|
Supplementary Table 8. The overlap summary of four SCN DEG sets in Figure 6A. The numbers in each cell follow the "A (B | C)" format, where A is the number of common DEGs, B is the number of common DEGs with the same direction of change, and C is the number of DEGs with opposite direction of change.

| DEG Sets           | db/+ vs db/+ PIO | db/+ vs db/db | db/+ PIO vs db/db PIO | db/db vs db/db PIO |
|--------------------|------------------|---------------|-----------------------|--------------------|
|                    | # DEGs           | 1182          | 1066                  | 2596               | 4537               |
| db/+ vs db/+ PIO   | 1182             | 1182 (1182 | 0)                   | 187 (149 | 38) | 374 (308 | 66) | 872 (867 | 5) |
| db/+ vs db/db      | 1066             | 187 (149 | 38) | 1066 (1066 | 0) | 452 (436 | 16) | 484 (161 | 323) |
| db/+ PIO vs db/db PIO | 2596           | 374 (308 | 66) | 452 (436 | 16) | 2596 (2596 | 0) | 1600 (1559 | 41) |
| db/db vs db/db PIO | 4537             | 872 (867 | 5) | 484 (161 | 323) | 1600 (1559 | 41) | 4537 (4537 | 0) |
**Supplementary Table 9.** The 20 most up-regulated genes and 20 most down-regulated genes that are dysregulated by diabetes and reversed by pioglitazone treatment in SCN. FC: fold-change; FDR: false discovery rate. Color indicates the up (red) or down (blue) regulation in the second group (eg. *db/db* in the *db/+* vs *db/db* comparison)

| GeneID | Symbol | Description | db/+ vs db/db | db/db vs db/db PIO |
|--------|--------|-------------|---------------|-------------------|
| 20284  | Scrg1  | scrapie responsive gene 1 | 3.17 | 7.9E-03 | -1.88 | 1.9E-02 |
| 240332 | Slc6a7 | solute carrier family 6 (neurotransmitter transporter, L-proline), member 7 | 3.07 | 1.7E-06 | -2.53 | 2.3E-06 |
| 24111  | Uts2   | urotensin 2 | 3.01 | 8.0E-05 | -1.58 | 5.9E-03 |
| 58222  | Rab37  | RAB37, member of RAS oncogene family | 2.50 | 1.5E-04 | -1.61 | 7.1E-03 |
| 66526  | Tceanc2 | RIKEN cDNA 2210012G02 gene | 2.50 | 2.0E-02 | -2.13 | 2.7E-02 |
| 223920 | Soat2  | sterol O-acyltransferase 2 | 2.48 | 9.1E-04 | -2.04 | 5.4E-04 |
| 21956  | Tnnt2  | troponin T2, cardiac | 2.33 | 1.1E-03 | -1.35 | 3.3E-02 |
| 11685  | Alox12e | arachidonate lipoxygenase, epidermal | 2.30 | 1.4E-04 | -1.84 | 8.4E-04 |
| 18039  | Nefl   | neurofilament, light polypeptide | 2.17 | 4.9E-04 | -2.10 | 2.9E-04 |
| 66809  | Krt20  | keratin 20 | 2.11 | 2.1E-03 | -1.42 | 2.5E-02 |
| 381319 | Batf3  | basic leucine zipper transcription factor, ATF-like 3 | 2.10 | 5.4E-04 | -1.51 | 8.0E-04 |
| 12659  | Ovgp1  | oviductal glycoprotein 1 | 2.10 | 4.4E-04 | -1.33 | 3.5E-02 |
| 11601  | Angpt2 | angiopoietin 2 | 2.07 | 4.0E-03 | -1.78 | 2.7E-04 |
| 56747  | Sez6l  | seizure related 6 homolog like | 2.06 | 5.0E-03 | -1.62 | 2.3E-02 |
| 76640  | 1700113H08Rik | RIKEN cDNA 1700113H08 gene | 2.00 | 1.5E-02 | -1.72 | 4.7E-03 |
| 70571  | Tcerg1l | transcription elongation regulator 1-like | 1.99 | 1.5E-02 | -2.09 | 3.5E-03 |
| 235048 | Zfp599 | zinc finger protein 599 | 1.95 | 3.3E-02 | -2.01 | 2.2E-03 |
| 22360  | Nrsn1  | neurensin 1 | 1.95 | 1.1E-02 | -1.61 | 5.6E-03 |
| 11830  | Aqp5   | aquaporin 5 | 1.92 | 1.3E-02 | -2.92 | 4.0E-05 |
| 230678 | Tmem125 | transmembrane protein 125 | 1.89 | 2.6E-03 | -1.86 | 7.5E-04 |
| 17329  | Cxcl9  | chemokine (C-X-C motif) ligand 9 | -1.99 | 2.5E-02 | 11.06 | 8.6E-04 |
| 58805  | Mlxipl | MLX interacting protein-like | -2.01 | 3.5E-02 | 3.37 | 9.6E-05 |
| 20528  | Slc2a4 | solute carrier family 2 (facilitated glucose transporter), member 4 | -2.02 | 7.8E-03 | 3.51 | 8.2E-06 |
| 171180 | Syt12  | synaptotagmin XII | -2.06 | 4.1E-02 | 2.83 | 1.8E-05 |
| 22117  | Tst    | thiosulfate sulfurtransferase, mitochondrial | -2.08 | 1.4E-04 | 2.19 | 1.2E-05 |
| 58200  | Ppp1r1a | protein phosphatase 1, regulatory (inhibitor) subunit 1A | -2.19 | 2.3E-03 | 8.21 | 3.2E-07 |
### GeneID | Symbol | Description | db/+ vs db/db | db/db vs db/db PIO |
|---------|--------|-------------|---------------|--------------------|
| 21835   | Thrsp  | thyroid hormone responsive SPOT14 homolog (Rattus) | -2.28 1.5E-02 | 3.67 7.8E-06 |
| 104158  | Ces1d  | carboxylesterase 1D | -2.32 2.2E-02 | 2.95 1.7E-03 |
| 53311   | Mybph  | myosin binding protein H | -2.36 1.9E-03 | 1.77 2.6E-03 |
| 26464   | Vnn3   | vanin 3 | -2.39 2.4E-02 | 2.23 3.7E-03 |
| 13106   | Cyp2e1 | cytochrome P450, family 2, subfamily e, polypeptide 1 | -2.53 3.0E-04 | 3.28 8.2E-06 |
| 83961   | Nrg4   | neuregulin 4 | -2.64 5.2E-03 | 4.77 2.5E-05 |
| 170786  | Cd209a | CD209a antigen | -2.68 4.6E-03 | 1.79 4.8E-02 |
| 243270  | Gpr81  | G protein-coupled receptor 81 | -2.77 4.1E-02 | 2.04 1.7E-02 |
| 12683   | Cidea  | cell death-inducing DNA fragmentation factor, alpha subunit-like effector A | -2.82 9.8E-03 | 71.60 2.5E-07 |
| 18534   | Pck1   | phosphoenolpyruvate carboxykinase 1, cytosolic | -3.07 1.5E-02 | 2.90 1.4E-03 |
| 234564  | Ces1f  | carboxylesterase 1F | -5.27 5.0E-03 | 7.16 8.5E-04 |
| 68393   | Mogat1 | monoacylglycerol O-acyltransferase 1 | -5.47 8.0E-05 | 1.89 1.2E-03 |
| 20319   | Sfrp2  | secreted frizzled-related protein 2 | -5.48 1.4E-04 | 3.73 1.1E-04 |
| 13107   | Cyp2f2 | cytochrome P450, family 2, subfamily f, polypeptide 2 | -30.87 1.6E-10 | 3.63 6.4E-04 |
**Supplementary Table 10.** The 20 most up-regulated genes and 20 most down-regulated genes that are dysregulated by diabetes and exacerbated by pioglitazone treatment in SCN. FC: fold-change; FDR: false discovery rate. Color indicates the up (red) or down (blue) regulation in the second group (e.g. db/db in the db/+ vs db/db comparison)

| GeneID | Symbol | Description                                                                 | db/+ vs db/db | db/db vs db/db PIO |
|--------|--------|-----------------------------------------------------------------------------|---------------|-------------------|
| 93726  | Ear11  | eosinophil-associated, ribonuclease A family, member 11                     | 26.17         | 1.2E-03           |
| 24108  | Ubd    | ubiquitin D                                                                  | 8.57          | 3.2E-03           |
| 67717  | Lipf   | lipase, gastric                                                              | 6.46          | 1.9E-02           |
| 381974 | Mrgrpg | MAS-related GPR, member G                                                     | 5.44          | 1.9E-03           |
| 16009  | Igfbp3 | insulin-like growth factor binding protein 3                                 | 3.54          | 1.1E-04           |
| 11425  | Apoc4  | apolipoprotein C-IV                                                          | 3.35          | 1.9E-03           |
| 11813  | Apoc2  | apolipoprotein C-II                                                          | 3.25          | 9.5E-03           |
| 433470 | AA467197| expressed sequence AA467197                                                 | 2.78          | 8.4E-03           |
| 17896  | Myl4   | myosin, light polypeptide 4                                                  | 2.17          | 7.3E-03           |
| 16846  | Lep    | leptin                                                                       | 2.15          | 8.2E-03           |
| 13723  | Emb    | embigin                                                                      | 2.14          | 3.2E-02           |
| 213696 | Duoxa1 | dual oxidase maturation factor 1                                              | 2.04          | 1.2E-03           |
| 21857  | Timp1  | tissue inhibitor of metalloproteinase 1                                       | 1.89          | 1.6E-02           |
| 21906  | Otop1  | otopetrin 1                                                                  | 1.85          | 7.3E-03           |
| 20753  | Spr1a  | small proline-rich protein 1A                                                | 1.80          | 2.6E-02           |
| 15484  | Hsd11b2| hydroxysteroid 11-beta dehydrogenase 2                                      | 1.80          | 9.9E-03           |
| 14168  | Fgf13  | fibroblast growth factor 13                                                  | 1.77          | 1.5E-02           |
| 68453  | Gpihbp1| GPI-anchored HDL-binding protein 1                                            | 1.73          | 1.1E-02           |
| 12534  | Cdk1   | cyclin-dependent kinase 1                                                    | 1.72          | 4.3E-02           |
| 232599 | Gm4876 | predicted gene 4876                                                          | 1.65          | 1.0E-02           |
| 14706  | Gng4   | guanine nucleotide binding protein (G protein), gamma 4                       | -1.64         | 4.6E-03           |
| 72324  | Plxdc1 | plexin domain containing 1                                                   | -1.65         | 8.2E-03           |
| 384009 | Glipr2 | GLI pathogenesis-related 2                                                   | -1.65         | 1.4E-02           |
| 19275  | Ptprn  | protein tyrosine phosphatase, receptor type, N                               | -1.73         | 5.9E-03           |
| 12578  | Cdkn2a | cyclin-dependent kinase inhibitor 2A                                          | -1.75         | 8.0E-03           |
| 244654 | Mtss1l | metastasis suppressor 1-like                                                | -1.80         | 1.3E-02           |
## SUPPLEMENTARY DATA

| GeneID | Symbol | Description                                      | db/+ vs db/db | db/db vs db/db PIO |
|--------|--------|--------------------------------------------------|---------------|--------------------|
|        |        | **GeneID** | **Symbol** | **Description** | **FC** | **FDR** | **FC** | **FDR** |
| 11514  | Adcy8  | adenylate cyclase 8                              | -1.80         | 6.2E-03            | -2.00  | 2.2E-03 |
| 11537  | Cfd    | complement factor D (adipsin)                    | -1.81         | 6.3E-04            | -1.65  | 2.1E-03 |
| 170741 | Plirb1 | paired immunoglobulin-like type 2 receptor beta 1 | -1.89         | 1.9E-02            | -1.95  | 4.3E-04 |
| 64082  | Popdc2 | popeye domain containing 2                       | -1.90         | 1.1E-02            | -1.63  | 3.5E-02 |
| 104885 | Tmem179| transmembrane protein 179                        | -1.92         | 8.3E-03            | -2.02  | 2.4E-05 |
| 80891  | Fcrls  | Fc receptor-like S, scavenger receptor           | -1.99         | 1.5E-03            | -2.10  | 7.7E-05 |
| 19242  | Ptn    | pleiotrophin                                     | -2.12         | 1.2E-02            | -1.78  | 1.4E-03 |
| 13138  | Dag1   | dystroglycan 1                                   | -2.21         | 4.4E-02            | -1.62  | 1.3E-03 |
| 66198  | Them5  | thioesterase superfamily member 5                | -2.21         | 1.1E-04            | -1.69  | 3.8E-03 |
| 12970  | Crygs  | crystallin, gamma S                              | -2.31         | 4.6E-03            | -1.63  | 1.6E-02 |
| 20983  | Syt4   | synaptotagmin IV                                 | -2.79         | 1.1E-04            | -1.50  | 1.3E-02 |
| 12824  | Col2a1 | collagen, type II, alpha 1                       | -2.89         | 5.0E-04            | -3.49  | 3.1E-05 |
| 17395  | Mmp9   | matrix metallopeptidase 9                        | -3.45         | 2.1E-04            | -1.61  | 2.6E-02 |
| 18979  | Pon1   | paraoxonase 1                                    | **-16.82**    | 4.1E-08            | -2.57  | 1.3E-03 |
**Supplementary Table 11.** The 20 most up-regulated genes and 20 most down-regulated genes that are dysregulated only by diabetes (db/+ vs db/db) and not by pioglitazone treatment in SCN. FC: fold-change; FDR: false discovery rate.

| GeneID | Symbol | Description | FC   | FDR    |
|--------|--------|-------------|------|--------|
| 17381  | Mmp12  | matrix metallopeptidase 12 | 44.77 | 1.3E-04 |
| 216343 | Tph2   | tryptophan hydroxylase 2 | 11.70 | 1.1E-03 |
| 16411  | Itgax  | integrin alpha X | 9.52 | 8.3E-04 |
| 242341 | Atp6v0d2 | ATPase, H+ transporting, lysosomal V0 subunit D2 | 9.13 | 5.5E-04 |
| 71760  | Agxt2l1 | alanine-glyoxylate aminotransferase 2-like 1 | 6.39 | 4.1E-08 |
| 14068  | F7     | coagulation factor VII | 6.10 | 3.3E-03 |
| 16197  | Il7r   | interleukin 7 receptor | 6.00 | 1.8E-03 |
| 17474  | Clec4d | C-type lectin domain family 4, member d | 5.28 | 3.6E-03 |
| 11501  | Adam8  | a disintegrin and metallopeptidase domain 8 | 5.24 | 2.1E-03 |
| 18430  | Oxtr   | oxytocin receptor | 5.11 | 5.0E-04 |
| 232680 | Cpa2   | carboxypeptidase A2, pancreatic | 4.97 | 9.5E-03 |
| 75766  | Dcstamp | transmembrane 7 superfamily member 4 | 4.33 | 7.5E-03 |
| 50778  | Rgs1   | regulator of G-protein signaling 1 | 4.14 | 1.4E-02 |
| 50765  | Tfr2   | transferrin receptor 2 | 4.08 | 2.3E-03 |
| 12309  | S100g  | S100 calcium binding protein G | 3.84 | 6.5E-04 |
| 12523  | Cd84   | CD84 antigen | 3.84 | 7.8E-03 |
| 278180 | Vsig4  | V-set and immunoglobulin domain containing 4 | 3.35 | 8.2E-03 |
| 234421 | Cib3   | calcium and integrin binding family member 3 | 3.27 | 1.4E-04 |
| 56857  | Slc37a2 | solute carrier family 37 (glycerol-3-phosphate transporter), member 2 | 3.21 | 8.3E-04 |
| 109648 | Npy    | neuropeptide Y | 3.09 | 2.1E-03 |
| 13003  | Vcan   | versican | -1.95 | 3.5E-05 |
| 56811  | Dkk2   | dickkopf homolog 2 (Xenopus laevis) | -1.95 | 2.4E-02 |
| 57764  | Ntn4   | netrin 4 | -1.96 | 1.8E-03 |
| 50786  | Hs6st2 | heparan sulfate 6-O-sulfotransferase 2 | -1.98 | 2.1E-03 |
| 16005  | Igfals | insulin-like growth factor binding protein, acid labile subunit | -2.04 | 3.4E-02 |
| 74342  | Lrmt1  | leucine rich repeat transmembrane neuronal 1 | -2.04 | 4.4E-03 |
| 24110  | Usp18  | ubiquitin specific peptidase 18 | -2.08 | 4.8E-04 |
| 16668  | Krt18  | keratin 18 | -2.11 | 2.4E-03 |
### SUPPLEMENTARY DATA

| GeneID  | Symbol   | Description                                                | FC   | FDR      |
|---------|----------|------------------------------------------------------------|------|----------|
| 319783  | A730056A06Rik | RIKEN cDNA A730056A06 gene                                  | -2.27| 2.6E-02  |
| 233271  | Luzp2    | leucine zipper protein 2                                    | -2.34| 5.2E-03  |
| 19662   | Rbp4     | retinol binding protein 4, plasma                           | -2.35| 2.5E-03  |
| 14172   | Fgf18    | fibroblast growth factor 18                                 | -2.35| 9.5E-03  |
| 11657   | Alb      | albumin                                                    | -2.44| 1.5E-02  |
| 64661   | Krtdap   | keratinocyte differentiation associated protein             | -2.58| 3.0E-03  |
| 71412   | Dhrs2    | dehydrogenase/reductase member 2                            | -2.60| 1.1E-04  |
| 330908  | Opcml    | opioid binding protein/cell adhesion molecule-like          | -2.67| 9.1E-04  |
| 56471   | Stmn4    | stathmin-like 4                                            | -2.68| 2.8E-03  |
| 69123   | Eci3     | RIKEN cDNA 1810022C23 gene                                  | -2.81| 3.4E-03  |
| 11556   | Adrb3    | adrenergic receptor, beta 3                                 | -2.82| 5.7E-03  |
| 16178   | Il1r2    | interleukin 1 receptor, type II                             | -2.96| 7.8E-03  |
Supplementary Table 12. The 20 most up-regulated genes and 20 most down-regulated genes that are dysregulated only by pioglitazone treatment (db/db vs db/db PIO) and not by diabetes (db/+ vs db/db) in SCN. FC: fold-change; FDR: false discovery rate.

| GeneID  | Symbol | Description                                                                 | FC    | FDR       |
|---------|--------|------------------------------------------------------------------------------|-------|-----------|
| 22227   | Ucp1   | uncoupling protein 1 (mitochondrial, proton carrier)                         | 146.47| 2.5E-08   |
| 12686   | Elovl3 | elongation of very long chain fatty acids (FEN1/Elo2, SUR4/Elo3, yeast)-like 3 | 125.66| 4.2E-10   |
| 232493  | Gys2   | glycogen synthase 2                                                          | 32.25 | 2.3E-08   |
| 67758   | Aadac  | arylacetamide deacetylase (esterase)                                        | 29.90 | 4.0E-08   |
| 228677  | Sptlc3 | serine palmitoyltransferase, long chain base subunit 3                       | 27.72 | 2.2E-10   |
| 78977   | Popdc3 | popeye domain containing 3                                                   | 26.71 | 2.6E-07   |
| 12869   | Cox8b  | cytochrome c oxidase, subunit VIIIb                                          | 16.95 | 2.0E-05   |
| 13088   | Cyp2b10| cytochrome P450, family 2, subfamily b, polypeptide 10                       | 15.33 | 7.9E-06   |
| 13004   | Ncan   | neurocan                                                                     | 11.07 | 3.8E-06   |
| 107146  | Glyat  | glycine-N-acyltransferase                                                    | 10.66 | 9.4E-04   |
| 66968   | Plin5  | perilipin 5                                                                  | 10.01 | 3.4E-06   |
| 68172   | Rpl39l | ribosomal protein L39-like                                                   | 9.92  | 2.2E-03   |
| 11489   | Adam12 | a disintegrin and metallopeptidase domain 12 (meltrin alpha)                | 9.48  | 7.9E-07   |
| 268345  | Knc2   | potassium voltage gated channel, Shaw-related subfamily, member 2           | 9.25  | 2.8E-06   |
| 74121   | Acoxl  | acyl-Coenzyme A oxidase-like                                                 | 9.04  | 1.8E-06   |
| 108812  | Als2cr12| amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 12 (human) | 8.51  | 1.5E-05   |
| 109245  | Lrrc39 | leucine rich repeat containing 39                                            | 7.89  | 1.2E-05   |
| 108078  | Olr1   | oxidized low density lipoprotein (lectin-like) receptor 1                    | 7.85  | 1.2E-04   |
| 105892  | 9030619P08Rik | RIKEN cDNA 9030619P08 gene                                                   | 7.71  | 1.2E-06   |
| 75552   | Paqr9  | progestin and adipoQ receptor family member IX                               | 7.19  | 4.3E-06   |
| 56839   | Lgi1   | leucine-rich repeat LGI family, member 1                                     | -2.36 | 1.3E-05   |
| 73720   | Cst6   | cystatin E/M                                                                  | -2.45 | 5.3E-05   |
| 209966  | Pgbd5  | piggyBac transposable element derived 5                                      | -2.46 | 8.6E-05   |
| 140703  | Emid1  | EMI domain containing 1                                                       | -2.46 | 1.7E-05   |
| 64385   | Cyp4f14| cytochrome P450, family 4, subfamily f, polypeptide 14                       | -2.48 | 8.4E-04   |
| 13516   | Epyc   | epiphycan                                                                    | -2.49 | 2.0E-03   |
| 22287   | Scgb1a1| secretoglobin, family 1A, member 1 (uteroglobin)                              | -2.49 | 1.0E-04   |
| 232345  | A2m    | alpha-2-macroglobulin                                                        | -2.49 | 2.1E-06   |

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