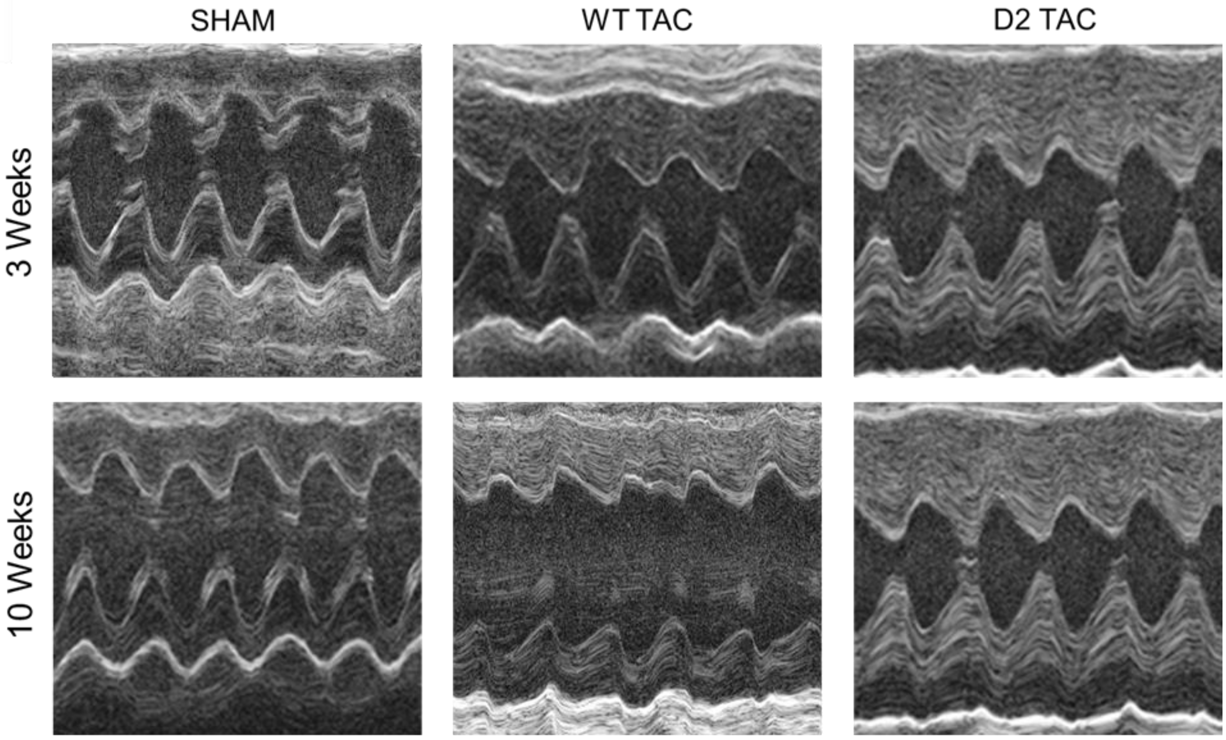
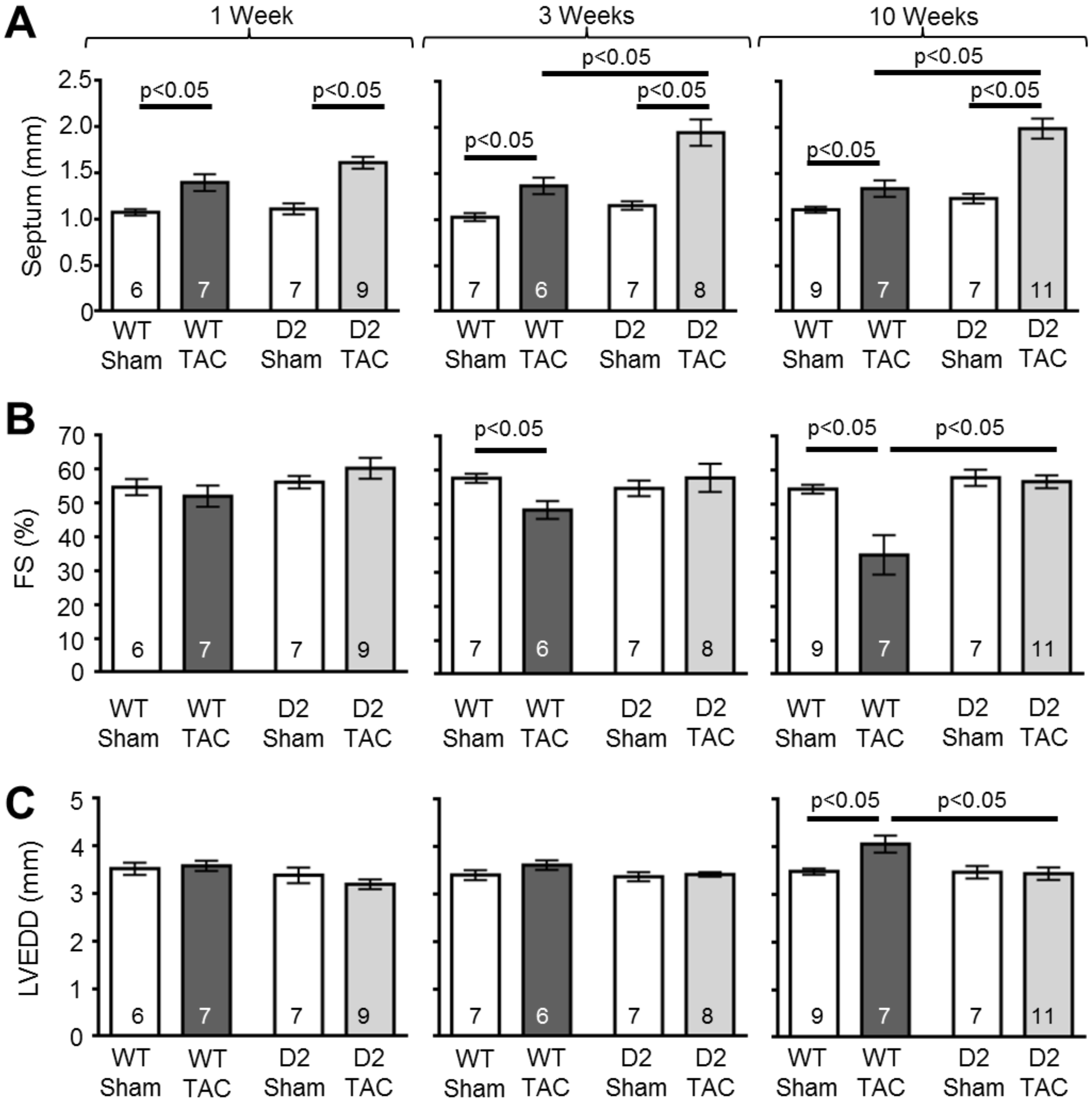
Supplemental Data for Toischer et al., "Cardiomyocyte proliferation prevents failure in pressure but not volume overload".

Contents:

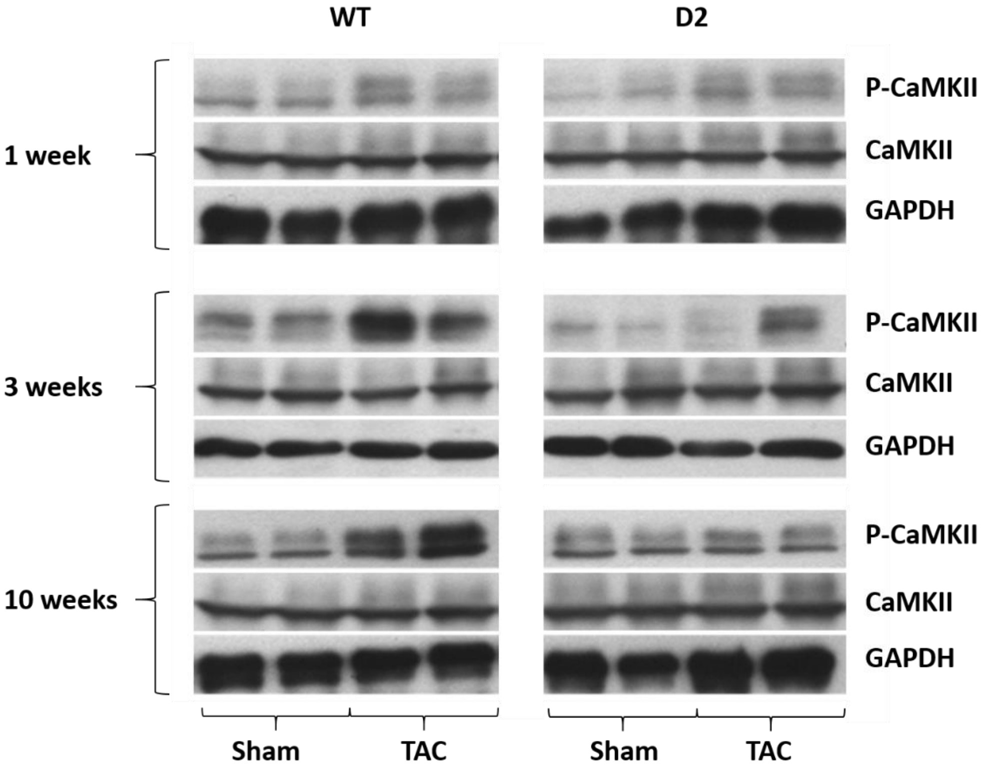
Supplemental Figure 1: Exaggerated hypertrophy in D2-TAC mice compared to WT-TAC. Representative echocardiographic recordings from a sham-operated, a WT-TAC and D2-TAC mice 3 and 10 weeks post-surgery (please note that the 10 week data set is identical to that shown in Figure 3E, and are repeated here to facilitate comparison to the 3 week data set).



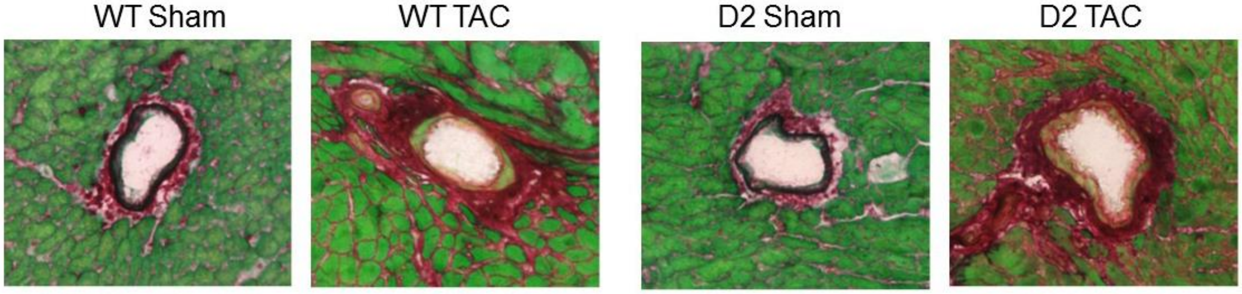
Supplemental Figure 2: Exaggerated hypertrophy in D2-TAC mice compared to WT-TAC. Echocardiographic phenotype after 1, 3 and 10 weeks following either sham or TAC surgery in WT and D2 mice. A) Septum thickness B) Fractional shortening (FS). C) Left ventricular end diastolic dimension (LVEDD). Statistical analyses: two-way analysis of variance (ANOVA) followed by the Bonferroni procedure.



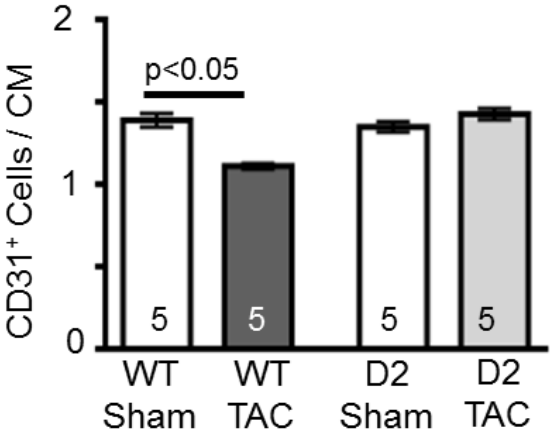
Supplemental Figure 3: Reduced CAMK2d activation in D2-TAC. Western blot example of phosphorylated CAMK2d, CAMK2d and GAPDH in WT and D2 mice 1, 3 and 10 weeks after TAC or Sham operation (CAMK2d and phosphorylated CAMK2d were obtained from parallel blots. GAPDH was analyzed in both blots). Data shown is from individual animals.



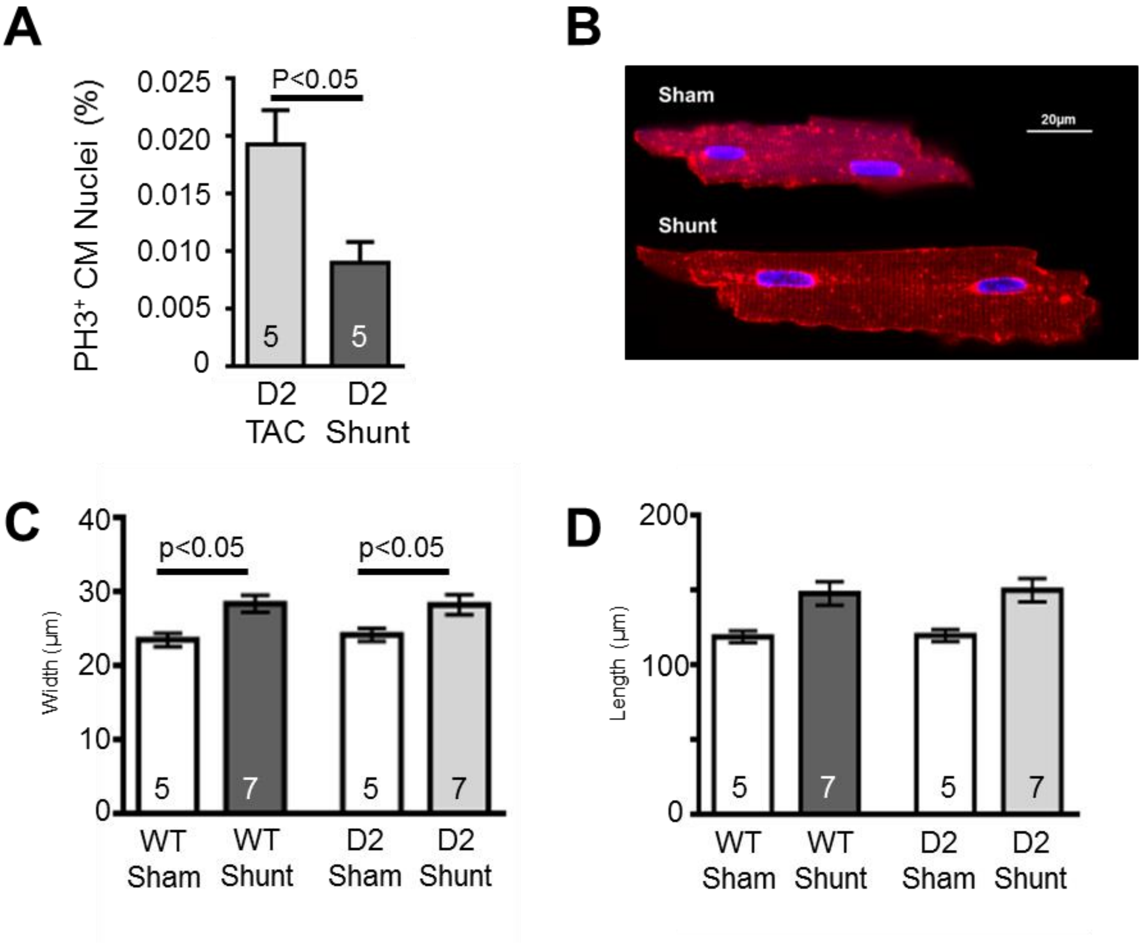
Supplemental Figure 4. No overt protection against TAC-induced perivascular fibrosis in D2 hearts.



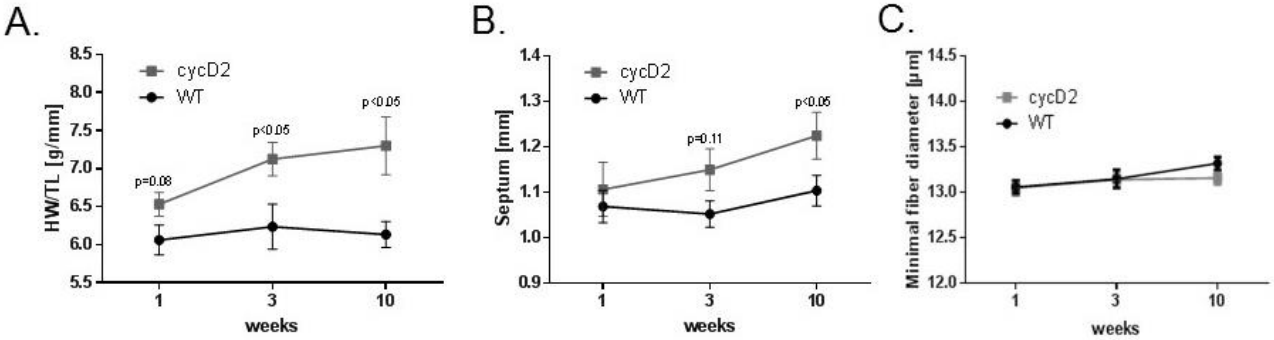
Supplemental Figure 5: Sustained capillarization of myocytes following TAC surgery in D2-TAC mice. Capillaries were identified by CD31 endothelial cell staining. Number of CD31 positive cells were related to cardiomyocyte numbers in sections. After 10 weeks number of capillaries per cardiomyocyte was reduced in WT-TAC but not in D2-TAC mice. Statistical analyses: two-way analysis of variance (ANOVA) followed by the Bonferroni procedure.



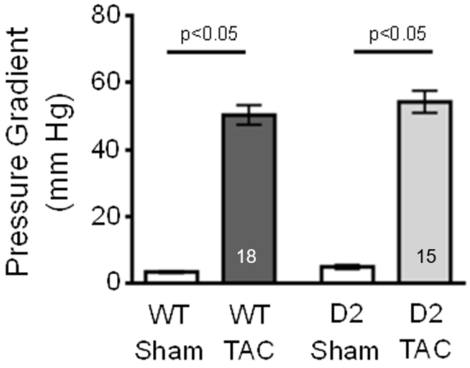
Supplemental Figure 6: Impact of Shunt on cardiomyocyte cell cycle activity and cell dimensions. A) Phosphorylated histone H3 (PH3) in D2-TAC vs. D2-Shunt (please note that the D2 TAC PH3 data is identical to that shown in Figure 4C, and is repeated here to facilitate comparison to the D2 Shunt PH3 data). B) Examples of isolated cardiomyocytes 10 weeks after Shunt. C) Measurement of cardiomyocyte width 10 weeks following sham or Shunt surgery in WT and D2 mice. D) Measurement of cardiomyocytes length 10 weeks following sham or Shunt surgery in WT and D2 mice. Statistical analyses: t-test for A, two-way analysis of variance (ANOVA) followed by the Bonferroni procedure for C+D.



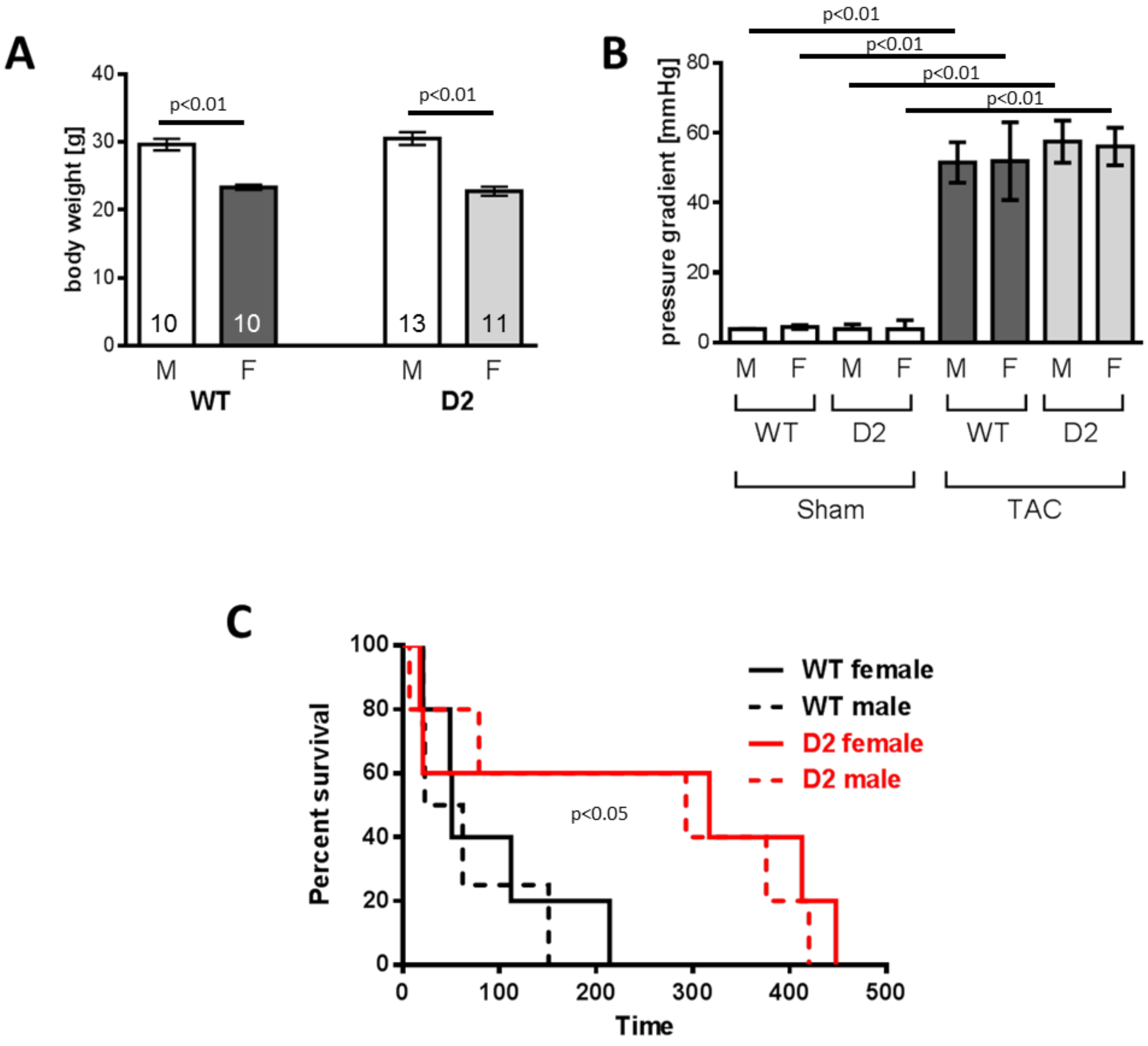
Supplemental Figure 7: Increases in cardiac mass in sham operated D2 mice occur largely after 9 weeks of age. (A) Plot of heart weight / tibia length (HW/TL) for sham operated wild type and sham operated D2 mice at 1, 3 and 10 weeks post-surgery (corresponding to 9 (n: WT 6 vs. D2 7), 12 (n: WT 7 vs. D2 7) and 18 (n: WT 9 vs. D2 7) weeks of age). (B) Plot of septum thickness (as determined via echocardiography) for the same time periods. (C) Plot of minimal cardiomyocyte fiber diameter (MFD) for the same time periods. Significant increases in cardiac mass are apparent only at 12 and 18 weeks of age (ie., at 3 and 10 weeks post-sham surgery, panels A and B). Since MFD was comparable between D2 and WT mice at all time points, these data argue that the increased mass in D2 mice reflects an increase in cardiomyocyte numbers, which occurred predominately between 9 and 18 weeks of age in the D2 mice. Statistical analyses: two-way analysis of variance (ANOVA).



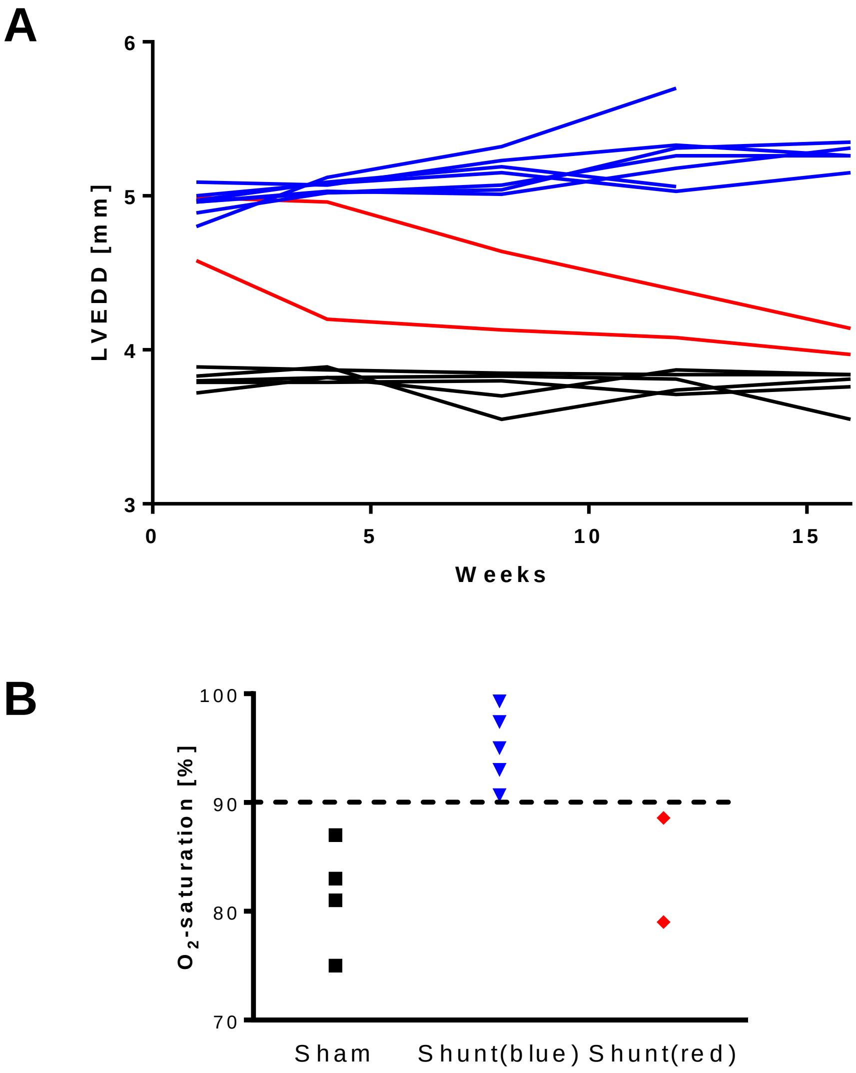
Supplemental Figure 8: Pressure gradient across the constricting ligature in WT and D2 mice following sham or TAC surgery (n=15/18/13/15). Statistical analyses: two-way analysis of variance (ANOVA) followed by the Bonferroni procedure.



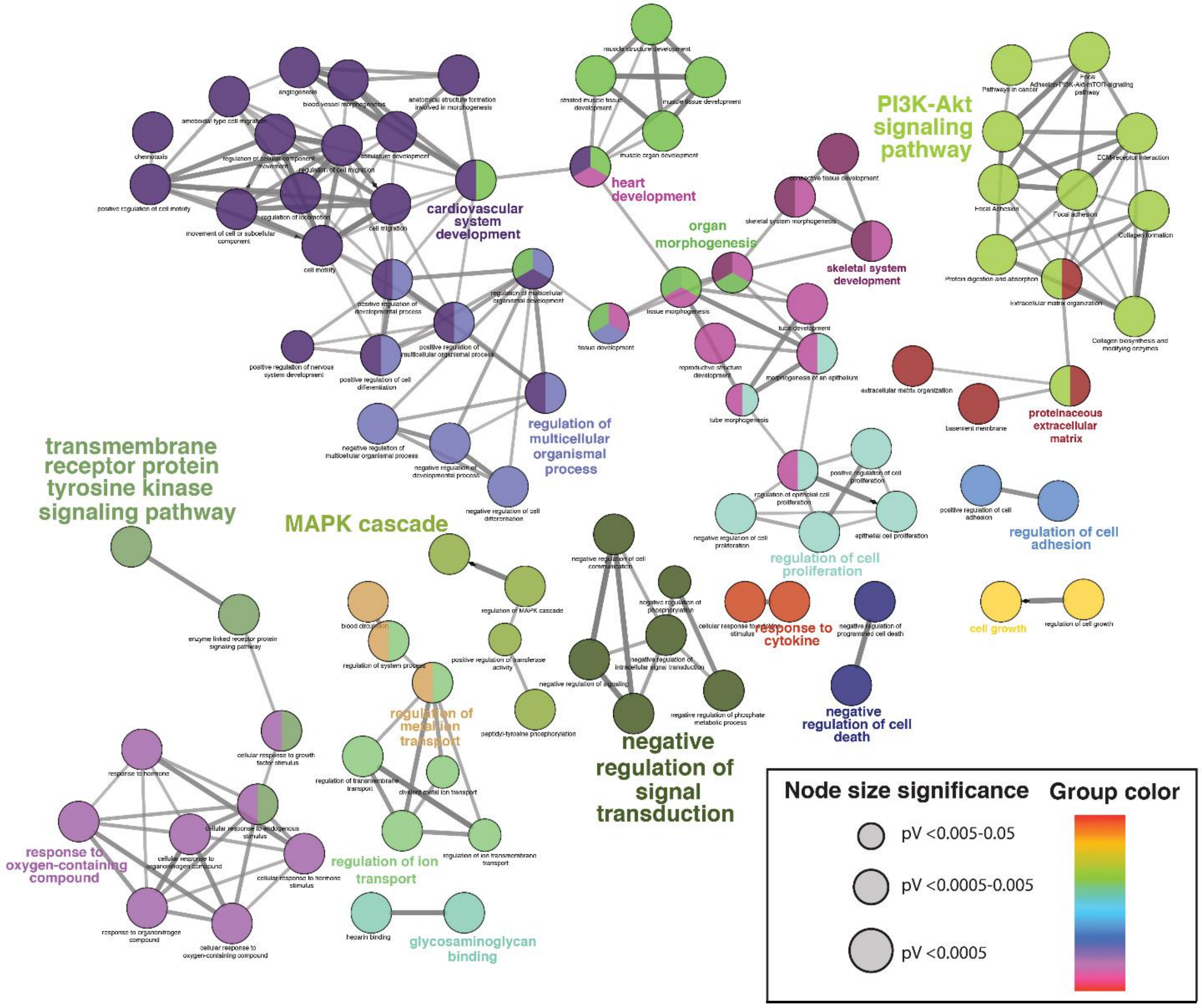
Supplemental Figure 9: Pressure gradients and survival of male and female WT and D2 mice subjected to sham or TAC surgery. A) Body weight of male and female WT and D2 animals. B) Pressure gradient across the constricting ligature in male and female WT and D2 mice following sham or TAC surgery (n=7/8/8/5/8/9/7/8). C) Survival plot of male (dashed line) or female (solid line) WT-TAC (black line; n: female 5, male 5), D2-TAC (red line; n: female 5, male 5). Statistical analyses: two-way analysis of variance (ANOVA) followed by the Bonferroni procedure.



Supplemental Figure 10: Patency of aortocaval Shunt by repeated measurement of LVEDD. A) Unpublished data from a previous study show that ~10% of Shunt operated mice show a decline of the left ventricular end diastolic diameter (LVEDD) over time (red lines). B) Measurement of right ventricular oxygen saturation was increased >90% in the mice following shunt surgery (data not shown). Oxygen saturation continued to be >90% in shunt operated mice with persistent left ventricular dilatation (blue lines). Oxygen saturation of shunt operated mice with normalization of LVEDD (red lines) and sham operated mice (black lines) was <90%. Data from individual animals is depicted.



Supplemental Figure 11: Pathway difference between D2-TAC and D2-Shunt mice. Network of differential regulated pathway from ClueGO analysis of significantly regulated genes in the transcriptomes of D2-TAC (n=3) vs. D2-shunt mice (n=5).



Supplemental Table 1: Differentially regulated cell cycle genes (determined by RNA-Seq and KEGG-pathway mmu04110 analysis, as well as by non-canonical candidate testing; WT n=5, D2-Sham n=5, D2-TAC n=3, D2-Shunt n=5).

WT vs. D2-Sham

gene name	baseMean	log2FoldChange	Padj
Ccnd2	281940	6,84	0
Cdkn2c	515	1,90	4,6E-121
Mcm2	608	2,39	1,01E-95
Mcm5	342	1,85	2,32E-41
Mcm7	317	1,27	8,63E-25
Mcm4	449	1,04	1,05E-24
Bub1b	64	1,51	8,58E-17
E2f1	71	1,29	3,44E-14
Cdc20	61	1,21	2,13E-10
Chek1	38	1,09	6,92E-08
Pitx2	12	1,229	1,06E-05

D2-Sham vs. D2-TAC

gene name	baseMean	log2FoldChange	padj
Myc	100	1,15	0,0003
Tgfb2	703	2,39	5,68E-29
Plk1	47	1,53	3,28E-08
Ccnb2	62	1,25	1,96E-06
Ttk	25	1,44	1,05E-05
Bub1	45	1,32	7,64E-05
Ccna2	167	1,13	0,0006
Ccnb1	26	1,16	0,0012
Cdkn1a	1588	1,06	0,0145
Wee1	485	-1,04	0,0173

D2-Sham vs. D2-Shunt

gene name	baseMean	log2FoldChange	padj
none			

D2-TAC vs. D2-Shunt

gene name	baseMean	log2FoldChange	padj
Myc	116	-1,03	0,0011
Tgfb2	815	-2,15	6,62E-23
Wee1	675	1,60	6,28E-08

Supplemental Table 2: Gene ontology/pathway term network from differential regulated genes in the transcriptomes of D2-TAC (n=3) vs. D2-shunt mice (n=5).

GOID	GOTerm	Nr. Genes	% Associated Genes	Term PValue Corrected with Bonferroni step down	Associated Genes Found
WP:85	Focal Adhesion	23	12,432432	8,90E-10	[Blk, Col11a1, Col1a1, Col1a2, Col3a1, Col4a1, Col4a4, Col5a1, Col5a2, Col5a3, Col6a2, Egfr, Fn1, Igf1, Itga11, Itga9, Itgb3, Lamb3, Lamc3, Pdgfc, Pik3r1, Thbs4, Tnc]
GO:0000165	MAPK cascade	36	5,4216866	1,41E-05	[Angpt1, Cbs, Ccl11, Ctgf, Cyr61, Dixdc1, Dok5, Dusp7, Edn3, Egfr, Erbb4, Ereg, Fgf18, Gdf15, Gdf6, Grm4, Hsph1, Igf1, Itgb3, Lepr, Lif, Lpar2, Mdfi, Myc, Myoc, Ngfr, Per1, Pla2g5, Plvap, Rgs2, Sfrp1, Sfrp2, Sox9, Tbc1d10c, Tgfb2, Wnk2]
GO:0001501	skeletal system development	40	8,492569	1,37E-11	[Acan, Cbs, Col11a1, Col1a1, Col1a2, Col5a2, Ctgf, Cyr61, Dnm3os, Fbn1, Fbn2, Fgf18, Fgf6, Foxc2, Frem1, Fst, Igf1, Loxl3, Mdfi, Mgp, Mmp14, Mmp2, Myc, Myoc, Pdgfc, Prrx2, Pthlh, Rgn, Runx1, Scx, Sfrp1, Sfrp2, Sh3pxd2b, Snai1, Sox9, Sparc, Tbx15, Tgfb2, Twist1, Zbtb16]
GO:0001525	angiogenesis	36	8,759124	8,11E-11	[Ace, Amot, Angpt1, Ccl11, Ccl2, Col4a1, Col8a1, Col8a2, Ctgf, Cx3cl1, Cyp1b1, Cyr61, Ecm1, Egr3, Ereg, Esm1, Fgf18, Fgf6, Fn1, Foxc2, Hif3a, Hspb1, Itgb3, Lepr, Lif, Loxl3, Mmp2, Otulin, Ptgs2, Runx1, Serpinf1, Sfrp2, Sparc, Srpx2, Tnfrsf12a, Tnmd]
GO:0001558	regulation of cell growth	22	6,4327483	9,77E-05	[Cda, Cgref1, Ctgf, Cth, Cyr61, Enpp1, Esm1, Fbp2, Fhl1, Fn1, Igf1, Igfbp2, Igfbp6, Mmp14, Nppa, Nppb, Pi16, Sfrp1, Sfrp2, Slc25a33, Tgfb2, Tnfrsf12a]
GO:0001667	ameboidal-type cell migration	21	7,118644	4,72E-05	[Amot, Angpt1, Cyp1b1, Edn3, Egr3, Erbb4, Fgf18, Fgf7, Foxc2, Has1, Hspb1, Itgb3, Loxl3, Ptgs2, Serpinf1, Sox9, Sparc, Srpx2, Tgfb2, Timp1, Twist1]
GO:0001944	vasculature development	47	7,8202996	2,24E-12	[Ace, Aldh1a2, Amot, Angpt1, Ccl11, Ccl2, Col1a1, Col1a2, Col3a1, Col4a1, Col5a1, Col8a1, Col8a2, Ctgf, Cx3cl1, Cyp1b1, Cyr61, Ecm1, Egr3, Ereg, Esm1, Fgf18, Fgf6, Fn1, Foxc2, Foxs1, Hif3a, Hspb1, Igf1, Itgb3, Lepr, Lif, Lox, Loxl3, Mmp2, Otulin, Prrx2, Ptgs2, Runx1, Serpinf1, Sfrp2, Sparc, Srpx2, Tgfb2, Tnfrsf12a, Tnmd, Wnt2]
GO:0002009	morphogenesis of an epithelium	31	6,2	5,69E-06	[Aldh1a2, Angpt1, Ccl11, Col4a1, Col5a1, Cthrc1, Cyr61, Egfr, Enah, Etv4, Fgf7, Foxc2, Fst, Igf1, Lif, Mgp, Mmp14, Mmp2, Myc, Ngfr, Pthlh, Runx1, Sfrp1, Sfrp2, Snai1, Sox9, St14, Tgfb2, Tnc, Twist1, Wnt2]
WP:2841	Focal Adhesion-PI3K-Akt-mTOR-signaling pathway	33	10,091743	1,63E-11	[Angpt1, Col11a1, Col1a1, Col1a2, Col3a1, Col4a1, Col4a4, Col5a1, Col5a2, Col5a3, Col6a2, Creb3l1, Egfr, Fgf18, Fgf6, Fgf7, Fn1, Gng8, Hif3a, Igf1, Irs3, Itga11, Itga9, Itgb3, Lamb3, Lamc3, Lpar2, Ngfr, Pdgfc, Pfkfb1, Pik3r1, Thbs4, Tnc]
KEGG:04151	PI3K-Akt signaling pathway	34	9,60452	2,79E-11	[Angpt1, Col11a1, Col1a1, Col1a2, Col3a1, Col4a1, Col4a4, Col5a1, Col5a2, Col5a3, Col6a1, Col6a2, Col6a3, Col6a5, Creb3l1, Egfr, Fgf18, Fgf6, Fgf7, Fn1,

					Gng8, Igf1, Itga11, Itga9, Itgb3, Lamb3, Lamc3, Lpar2, Myc, Ngfr, Pdgfc, Pik3r1, Thbs4, Tnc]
KEGG:04510	Focal adhesion	26	12,5	4,09E-11	[Col11a1, Col1a1, Col1a2, Col3a1, Col4a1, Col4a4, Col5a1, Col5a2, Col5a3, Col6a1, Col6a2, Col6a3, Col6a5, Egfr, Fn1, Igf1, Itga11, Itga9, Itgb3, Lamb3, Lamc3, Pdgfc, Pik3r1, Shc4, Thbs4, Tnc]
KEGG:04512	ECM-receptor interaction	22	25	1,00E-15	[Col11a1, Col1a1, Col1a2, Col3a1, Col4a1, Col4a4, Col5a1, Col5a2, Col5a3, Col6a1, Col6a2, Col6a3, Col6a5, Fn1, Itga11, Itga9, Itgb3, Lamb3, Lamc3, Sdc1, Thbs4, Tnc]
KEGG:04974	Protein digestion and absorption	20	22,47191	2,74E-13	[Col11a1, Col12a1, Col15a1, Col1a1, Col1a2, Col22a1, Col3a1, Col4a1, Col4a4, Col5a1, Col5a2, Col5a3, Col6a1, Col6a2, Col6a3, Col6a5, Col9a2, Eln, Slc1a1, Slc8a2]
KEGG:05200	Pathways in cancer	23	5,793451	2,67E-04	[Arnt2, Col4a1, Col4a4, Egfr, Fgf18, Fgf6, Fgf7, Fn1, Gng8, Igf1, Lamb3, Lamc3, Lpar2, Mmp2, Myc, Pik3r1, Plcg2, Ptgs2, Runx1, Tgfb2, Wnt2, Wnt5b, Zbtb16]
GO:0005539	glycosaminoglycan binding	24	13,333333	7,53E-11	[Acan, Adamts8, Bgn, Ccdc80, Ccl2, Col5a1, Col5a3, Ctgf, Cyr61, Dpysl3, Egflam, Fgf7, Fn1, Fstl1, Gpnmb, Ltbp2, Mdk, Pcolce, Pla2g5, Postn, Ptn, Sfrp1, Thbs4, Tpsb2]
GO:0005578	proteinaceous extracellular matrix	70	20,289856	2,40E-45	[Acan, Adamts20, Adamts4, Adamts8, Adamtsl2, Bgn, Ccdc80, Col11a1, Col12a1, Col15a1, Col16a1, Col1a1, Col1a2, Col26a1, Col3a1, Col4a1, Col4a4, Col5a1, Col5a2, Col5a3, Col6a1, Col6a2, Col6a3, Col6a5, Col8a1, Col8a2, Col9a2, Ctgf, Cthrc1, Cyr61, Ecm1, Egflam, Eln, Emilin1, Emilin2, Fbn1, Fbn2, Fn1, Frem1, Igf1, Lamb3, Lamc3, Lox, Loxl1, Loxl3, Mfap2, Mfap4, Mfap5, Mmp2, Mmp3, Myoc, P3h2, Postn, Ptn, Runx1, Serpinf1, Sfrp1, Snca, Sparc, Spon2, Tgfb2, Thbs4, Timp1, Timp3, Tnc, Tnfrsf11b, Vwa1, Vwc2, Wnt2, Wnt5b]
GO:0005604	basement membrane	27	25,233644	1,53E-19	[Acan, Ccdc80, Col15a1, Col4a1, Col4a4, Col5a1, Col8a1, Col8a2, Egflam, Fbn1, Fn1, Frem1, Lamb3, Lamc3, Loxl1, Loxl3, P3h2, Runx1, Serpinf1, Sparc, Tgfb2, Thbs4, Timp1, Timp3, Tnc, Vwa1, Vwc2]
GO:0006928	movement of cell or subcellular component	82	5,430464	7,53E-13	[Acan, Ace, Amot, Angpt1, Ccl11, Ccl2, Ccl21a, Celsr3, Col1a1, Col3a1, Col5a1, Ctgf, Cthrc1, Cx3cl1, Cyp1b1, Cyr61, Dixdc1, Dnaic1, Dpysl3, Drd1, Dsg2, Dynll1, Ecm1, Edn3, Efhc1, Efnb3, Egfr, Egr2, Egr3, Enah, Erbb4, Etv4, Fgf18, Fgf7, Fn1, Foxc2, Has1, Hspb1, Igf1, Itga11, Itga9, Itgb3, Kcnh2, Kif1a, Kif5c, Loxl3, Lrp8, Lrrc15, Mdk, Mmp14, Mmp2, Mmp3, Myoc, Neurl1a, Ngfr, Pik3r1, Plvap, Pou4f1, Ptgs2, Pvrl1, Rgn, Rnf207, Rras2, Sdc1, Serpinf1, Sfrp1, Sfrp2, Snai1, Sorbs2, Sox9, Sparc, Srgap3, Srpx2, St14, Tgfb2, Thbs4, Timp1, Tnfrsf12a, Ttll1, Tubb3, Twist1, Wnt5b]
GO:0006935	chemotaxis	27	5,9602647	5,16E-05	[Amot, Angpt1, Ccl11, Ccl2, Ccl21a, Ccrl2, Cx3cl1, Cxcr6, Cyr61, Edn3, Efnb3, Egr2, Egr3, Enah, Etv4, Fgf18, Fgf7, Fn1, Hspb1, Itga9, Itgb3, Kif5c, Ngfr, Pvrl1, Tgfb2, Thbs4, Tubb3]
GO:0007167	enzyme linked receptor protein signaling pathway	51	6,4803047	1,94E-10	[Adamts3, Adamtsl2, Afap1l2, Angpt1, Bex1, Blk, Ccl2, Col1a2, Col3a1, Ctgf, Cyr61, Dok5, Efnb3, Egfr, Enpp1, Erbb4, Ereg, Esm1, Fbn1, Fbn2, Fgf18, Fgf6, Fgf7, Foxc2, Fst, Fstl3, Gdf15, Gdf6, Hspb1, Igf1, Igfbp2, Igfbp6, Irs3, Lif, Myoc, Neurl1a, Ngef, Ngfr, Nppa, Pdgfc, Pik3r1, Ptprt, Scx, Sfrp1, Sfrp2, Sh2b2, Shc4, Snca, Sox9, Tgfb2, Vwc2]

GO:0007169	transmembrane receptor protein tyrosine kinase signaling pathway	34	6,9246435	1,37E-07	[Adamts3, Afap1l2, Angpt1, Bex1, Blk, Ccl2, Ctgf, Dok5, Efnb3, Egfr, Enpp1, Erbb4, Ereg, Esm1, Fgf18, Fgf6, Fgf7, Foxc2, Hspb1, Igf1, Igfbp2, Igfbp6, Irs3, Myoc, Neurl1a, Ngef, Ngfr, Pdgfc, Pik3r1, Ptprt, Sh2b2, Shc4, Snca, Sox9]
GO:0007507	heart development	25	5,2742615	3,88E-04	[Ace, Adam19, Aldh1a2, Angpt1, Ankrd1, Col11a1, Col3a1, Col5a1, Cyr61, Dsg2, Erbb4, Fbn1, Foxc2, Pi16, Pou4f1, Scx, Sfrp2, Sh3pxd2b, Snai1, Sox9, Tcap, Tgfb2, Twist1, Wnt2, Xirp2]
GO:0007517	muscle organ development	27	7,520891	9,09E-07	[Acta1, Angpt1, Ankrd1, Arntl, Cenpf, Col11a1, Col3a1, Des, Egr2, Eln, Erbb4, Foxc2, Gpcpd1, Hlf, Lif, Myc, Nr1d2, Nupr1, Pi16, Pou4f1, Rcan1, Scx, Tcap, Twist1, Usp2, Wnt2, Xirp2]
GO:0008015	blood circulation	25	6,097561	6,70E-05	[Ace, Amot, Angpt1, Cbs, Col1a2, Corin, Ctgf, Cx3cl1, Drd1, Dsg2, Edn3, Egfr, Foxc2, Gnao1, Kcne1, Kcnh2, Mmp2, Nppa, Nppb, Pik3r1, Ptgs2, Rgs2, Rnf207, Tcap, Tgfb2]
GO:0008201	heparin binding	20	14,705882	8,72E-10	[Adamts8, Ccdc80, Ccl2, Col5a1, Col5a3, Ctgf, Cyr61, Fgf7, Fn1, Fstl1, Gpnmb, Ltbp2, Mdk, Pcolce, Pla2g5, Postn, Ptn, Sfrp1, Thbs4, Tpsb2]
GO:0008284	positive regulation of cell proliferation	49	6,155779	3,02E-09	[Aldh1a2, Arnt2, Bex1, Ccl11, Ccl2, Cd276, Clec11a, Crlf1, Ctgf, Cthrc1, Cx3cl1, Cyr61, Ecm1, Edn3, Egfr, Egr3, Erbb4, Ereg, Esm1, Fgf18, Fgf6, Fgf7, Igf1, Igfbp2, Itgb3, Lif, Malat1, Myc, Nampt, Ngfr, Pdgfc, Plac8, Prrx2, Ptgs2, Pthlh, Ptn, Scx, Sfrp1, Sfrp2, Shc4, Slc25a33, Sox9, St8sia1, Tgfb2, Thbs4, Timp1, Tnc, Twist1, Wnt2]
GO:0008285	negative regulation of cell proliferation	35	5,852843	3,93E-06	[Aldh1a2, Cd276, Cth, Ctla4, Cyp1b1, Dhcr24, Erbb4, Ereg, Etv4, Igf1, Kctd11, Klf9, Lif, Myc, Neurl1a, Nppb, Nupr1, P3h2, Pik3r1, Prnp, Ptgds, Ptgs2, Ptprv, Rgn, Runx1, Serpinf1, Sfrp1, Sfrp2, Sox9, Sparc, Srpx, Tgfb2, Tnmd, Wnk2, Zbtb16]
GO:0009725	response to hormone	34	5,7724957	7,29E-06	[Adam19, Adh1, Aldob, Ass1, Blk, Cry2, Egfr, Egr2, Egr3, Enpp1, Foxc2, Gck, Gpr22, Irs3, Klf9, Lepr, Lox, Mmp14, Mmp2, Ngfr, Npc1, Nr1d1, Nr1d2, Nr3c2, Nr5a1, Pik3r1, Ptprv, Sfrp1, Sh2b2, Slc25a33, Slc27a1, Tgfb2, Timp1, Timp3]
GO:0009887	organ morphogenesis	60	6,3424945	6,30E-12	[Acan, Aldh1a2, Angpt1, Ankrd1, Atp8a2, Cbs, Ccl11, Col11a1, Col1a1, Col1a2, Col3a1, Col5a1, Col5a2, Col8a1, Col8a2, Corin, Crb1, Ctgf, Cthrc1, Cyr61, Egfr, Ereg, Etv4, Fbn2, Fgf18, Fgf6, Fgf7, Foxc2, Frem1, Fst, Gcnt4, Igf1, Lif, Mdfi, Mmp14, Mmp2, Myc, Ngfr, Pdgfc, Pou4f1, Prrx2, Pthlh, Ptn, Pvrl1, Rp1, Scx, Sfrp1, Sfrp2, Snai1, Sox9, T2, Tbx15, Tcap, Tgfb2, Tnc, Tnfrsf11b, Twist1, Wnt2, Wnt5b, Xirp2]
GO:0009888	tissue development	98	5,6943636	4,68E-17	[Abca12, Acan, Acta1, Adamts20, Aldh1a2, Angpt1, Ankrd1, Arntl, Atp8a2, Cbs, Ccdc67, Ccl11, Cd276, Cenpf, Ces1d, Col11a1, Col1a1, Col3a1, Col4a1, Col5a1, Col5a2, Corin, Cst6, Ctgf, Cthrc1, Cyp1b1, Cyr61, Dgat2, Dhcr24, Dnm3os, Dsg2, Ecm1, Edn3, Egfr, Egr2, Eln, Enah, Enpp1, Erbb4, Etv4, Fbn2, Fgf18, Fgf6, Fgf7, Fn1, Foxc2, Fst, Gcnt4, Gpcpd1, Hlf, Igf1, Igsf10, Insc, Itgb3, Kcne1, Klf15, Lamc3, Leo1, Lif, Loxl3, Meox1, Mgp, Mmp14, Mmp2, Myc, Ngfr, Nr1d2, Nr5a1, Nupr1, Pi16, Postn, Pou4f1, Ppl, Prrx2, Ptgs2, Pthlh, Ptn, Pvrl1, Rcan1, Rp1, Runx1, Sbno2, Scx, Sfrp1, Sfrp2, Sh3pxd2b, Snai1, Sox9, St14, Tcap, Tgfb2, Tnc, Tnmd, Twist1, Usp2, Wnt2, Xirp2, Zbtb16]

GO:0009968	negative regulation of signal transduction	47	5,0865803	2,09E-06	[Adamtsl2, Arntl, Corin, Creb3l1, Cry2, Cth, Cthrc1, Cx3cl1, Dusp7, Ecm1, Enpp1, Faim2, Fbn1, Fbn2, Fbp2, Fst, Fstl3, Herpud1, Hspb1, Hsph1, Igf1, Kctd11, Lif, Mdfi, Mmp3, Myoc, Neurl1a, Ngfr, Nkd2, Nlrc3, Nr1d1, Per1, Prnp, Rgs2, Rgs7bp, Sfrp1, Sfrp2, Snai1, Snca, Sox9, Tbc1d10c, Tnfrsf23, Tnip3, Twist1, Vwc2, Wnk2, Wnt5b]
GO:0010243	response to organonitrogen compound	39	6,489185	5,98E-08	[Aldob, Blk, Cbs, Col16a1, Col1a1, Col1a2, Col3a1, Col4a1, Col5a2, Col6a1, Cry2, Drd1, Egfr, Egr2, Egr3, Enpp1, Foxc2, Gck, Gnao1, Gpr22, Irs3, Mmp2, Mmp3, Myc, Neurl1a, Ngfr, Panx1, Pdgfc, Per1, Pik3r1, Plcg2, Ptprv, Sfrp1, Sh2b2, Slc25a33, Slc26a6, Slc27a1, Snca, Sox9]
GO:0010648	negative regulation of cell communication	54	5,142857	1,67E-07	[Adamtsl2, Arntl, Corin, Creb3l1, Cry2, Cth, Cthrc1, Cx3cl1, Drd1, Dusp7, Ecm1, Edn3, Enpp1, Faim2, Fbn1, Fbn2, Fbp2, Fst, Fstl3, Gck, Herpud1, Hspb1, Hsph1, Igf1, Kctd11, Lif, Mdfi, Mmp3, Myoc, Neurl1a, Ngfr, Nkd2, Nlrc3, Npc1, Nr1d1, Per1, Pim3, Prnp, Ptgs2, Ptprv, Rgs2, Rgs7bp, Sfrp1, Sfrp2, Snai1, Snca, Sox9, Tbc1d10c, Tnfrsf23, Tnip3, Twist1, Vwc2, Wnk2, Wnt5b]
GO:0010959	regulation of metal ion transport	23	7,055215	2,12E-05	[Ace, Cacnb1, Drd1, Edn3, Fhl1, Gck, Gnao1, Gpr39, Igf1, Itgb3, Kcne1, Kcnh2, Nppa, Oprd1, Per1, Plcg2, Prnp, Ptgs2, Rgn, Rnf207, Snca, Tgfb2, Wnk2]
GO:0014706	striated muscle tissue development	27	7,2	2,07E-06	[Acta1, Aldh1a2, Angpt1, Ankrd1, Arntl, Cenpf, Col11a1, Dsg2, Egr2, Eln, Erbb4, Foxc2, Gpcpd1, Hlf, Myc, Nr1d2, Nupr1, Pi16, Pou4f1, Rcan1, Scx, Tcap, Tgfb2, Twist1, Usp2, Wnt2, Xirp2]
GO:0016049	cell growth	26	6,0465117	5,56E-05	[Cda, Cgref1, Ctgf, Cth, Cyr61, Emp1, Enpp1, Esm1, Fbp2, Fhl1, Fn1, Igf1, Igfbp2, Igfbp6, Itgb3, Mmp14, Nppa, Nppb, Nupr1, Pi16, Sfrp1, Sfrp2, Slc25a33, Sox9, Tgfb2, Tnfrsf12a]
GO:0016477	cell migration	65	5,9963098	6,99E-12	[Acan, Ace, Amot, Angpt1, Ccl11, Ccl2, Ccl21a, Celsr3, Col1a1, Col3a1, Col5a1, Ctgf, Cthrc1, Cx3cl1, Cyp1b1, Cyr61, Dixdc1, Dpysl3, Drd1, Ecm1, Edn3, Efhc1, Egfr, Egr3, Erbb4, Fgf18, Fgf7, Fn1, Foxc2, Has1, Hspb1, Igf1, Itga11, Itga9, Itgb3, Loxl3, Lrp8, Lrrc15, Mdk, Mmp14, Mmp2, Mmp3, Myoc, Pik3r1, Plvap, Pou4f1, Ptgs2, Rras2, Sdc1, Serpinf1, Sfrp1, Sfrp2, Snai1, Sorbs2, Sox9, Sparc, Srgap3, Srpx2, St14, Tgfb2, Thbs4, Timp1, Tnfrsf12a, Twist1, Wnt5b]
GO:0018108	peptidyl-tyrosine phosphorylation	21	6,7524114	7,99E-05	[Ace, Afap1l2, Angpt1, Blk, Cd4, Crlf1, Egfr, Erbb4, Ereg, Fgf7, Hsph1, Igf1, Itgb3, Lif, Lrp8, Neurl1a, Pdgfc, Sfrp1, Sfrp2, Thbs4, Wee1]
GO:0023057	negative regulation of signaling	53	5,0669217	3,63E-07	[Adamtsl2, Arntl, Corin, Creb3l1, Cry2, Cth, Cthrc1, Cx3cl1, Drd1, Dusp7, Ecm1, Edn3, Enpp1, Faim2, Fbn1, Fbn2, Fbp2, Fst, Fstl3, Gck, Herpud1, Hspb1, Hsph1, Igf1, Kctd11, Lif, Mdfi, Mmp3, Myoc, Neurl1a, Ngfr, Nkd2, Nlrc3, Nr1d1, Per1, Pim3, Prnp, Ptgs2, Ptprv, Rgs2, Rgs7bp, Sfrp1, Sfrp2, Snai1, Snca, Sox9, Tbc1d10c, Tnfrsf23, Tnip3, Twist1, Vwc2, Wnk2, Wnt5b]
GO:0030155	regulation of cell adhesion	36	6,405694	3,31E-07	[Angpt1, Ass1, Ccdc80, Ccl2, Cd276, Cd4, Col16a1, Col1a1, Col26a1, Col8a1, Ctla4, Cx3cl1, Cyp1b1, Cyr61, Egflam, Egr3, Emilin1, Foxc2, Fstl3, Hsph1, Igf1, Igfbp2, Itgb3, Lag3, Mmp14, Mmp2, Myoc, Pik3r1, Prnp, Ptn, Sox9, Tgfb2, Tnc, Tnfsf18, Vwc2, Zbtb16]
GO:0030198	extracellular matrix organization	36	17,647058	1,46E-20	[Acan, Adamts20, Bcl3, Ccdc80, Col11a1, Col1a1, Col1a2, Col3a1, Col4a1, Col4a4, Col5a1, Col5a2, Col5a3, Creb3l1, Ctgf, Cyp1b1, Cyr61, Egflam, Eln,

					Emilin1, Fn1, Foxc2, Has1, Lox, Loxl3, Mfap4, Mfap5, P4ha1, Postn, Scx, Sfrp2, Sh3pxd2b, Sox9, Tgfb2, Tnfrsf11b, Vwa1]
GO:0030334	regulation of cell migration	47	7,8333335	2,14E-12	[Acan, Ace, Amot, Angpt1, Ccl11, Ccl2, Ccl21a, Col1a1, Col3a1, Cx3cl1, Cyp1b1, Cyr61, Dpysl3, Drd1, Ecm1, Edn3, Egfr, Erbb4, Fgf18, Fgf7, Fn1, Foxc2, Has1, Hspb1, Igf1, Itgb3, Lrrc15, Mmp14, Mmp2, Mmp3, Myoc, Pik3r1, Plvap, Ptgs2, Rras2, Serpinf1, Sfrp1, Sfrp2, Snai1, Sox9, Sparc, Srgap3, Srpx2, Tgfb2, Thbs4, Timp1, Wnt5b]
GO:0032870	cellular response to hormone stimulus	24	5,714286	2,39E-04	[Blk, Egfr, Egr2, Egr3, Enpp1, Foxc2, Gck, Gpr22, Irs3, Klf9, Lepr, Mmp2, Ngfr, Npc1, Nr1d1, Nr1d2, Nr3c2, Nr5a1, Pik3r1, Ptprv, Sfrp1, Sh2b2, Slc25a33, Slc27a1]
GO:0034097	response to cytokine	27	5,283757	2,50E-04	[Aldh1a2, Angpt1, Ankrd1, Aqp4, Ccl2, Ccrl2, Col3a1, Cx3cl1, Cxcr6, Ecm1, Ereg, Fn1, Lepr, Nfil3, Plvap, Ptgs2, Ptprn, Rps6ka5, Sfrp1, Sh2b2, Slc26a6, Slc27a1, Snca, Star, Timp1, Timp3, Tnfsf18]
GO:0034762	regulation of transmembrane transport	22	5,6265984	3,83E-04	[Ace, Cacnb1, Cacng6, Clcn1, Edn3, Fhl1, Kcnd2, Kcne1, Kcnh2, Kcnh7, Kcnj3, Kcnj6, Kcnv2, Nppa, Plcg2, Prnp, Rgn, Rnf207, Shank1, Slc26a6, Twist1, Wnk2]
GO:0034765	regulation of ion transmembrane transport	20	5,347594	8,22E-04	[Ace, Cacnb1, Cacng6, Clcn1, Edn3, Fhl1, Kcnd2, Kcne1, Kcnh2, Kcnh7, Kcnj3, Kcnj6, Kcnv2, Nppa, Plcg2, Prnp, Rgn, Rnf207, Shank1, Wnk2]
GO:0035239	tube morphogenesis	21	5,316456	9,35E-04	[Aldh1a2, Angpt1, Ccl11, Col4a1, Cthrc1, Egfr, Enah, Etv4, Foxc2, Igf1, Mgp, Mmp14, Myc, Pthlh, Sfrp1, Sfrp2, Sox9, St14, Tnc, Twist1, Wnt2]
GO:0035295	tube development	33	5,28	5,44E-05	[Abca12, Ace, Aldh1a2, Angpt1, Ccl11, Clmp, Col3a1, Col4a1, Ctgf, Cthrc1, Egfr, Enah, Etv4, Fgf18, Fgf7, Foxc2, Igf1, Insc, Lif, Lox, Mgp, Mmp14, Myc, Pdgfc, Pthlh, Sfrp1, Sfrp2, Sox9, Sparc, St14, Tnc, Twist1, Wnt2]
GO:0040012	regulation of locomotion	50	7,1530757	9,75E-12	[Acan, Ace, Amot, Angpt1, Ccl11, Ccl2, Ccl21a, Col1a1, Col3a1, Cx3cl1, Cyp1b1, Cyr61, Dpysl3, Drd1, Ecm1, Edn3, Egfr, Erbb4, Fgf18, Fgf7, Fn1, Foxc2, Has1, Hspb1, Igf1, Itgb3, Lrrc15, Mmp14, Mmp2, Mmp3, Myoc, Pik3r1, Plvap, Ptgs2, Rgn, Rras2, Serpinf1, Sfrp1, Sfrp2, Snai1, Snca, Sox9, Sparc, Srgap3, Srpx2, Tgfb2, Thbs4, Timp1, Twist1, Wnt5b]
GO:0042127	regulation of cell proliferation	78	5,5084743	1,72E-12	[Ace, Aldh1a2, Angpt1, Arnt2, Bex1, Blk, Ccl11, Ccl2, Cd276, Clec11a, Crlf1, Ctgf, Cth, Cthrc1, Ctla4, Cx3cl1, Cyp1b1, Cyr61, Dhcr24, Ecm1, Edn3, Egfr, Egr3, Erbb4, Ereg, Esm1, Etv4, Fgf18, Fgf6, Fgf7, Igf1, Igfbp2, Itgb3, Kctd11, Klf9, Lif, Malat1, Myc, Nampt, Neurl1a, Ngfr, Nppb, Nr1d1, Nr3c2, Nupr1, P3h2, Pdgfc, Pik3r1, Plac8, Prnp, Prrx2, Ptgds, Ptgs2, Pthlh, Ptn, Ptprv, Rgn, Runx1, Scx, Serpinf1, Sfrp1, Sfrp2, Shc4, Slc25a33, Sox9, Sparc, Srpx, St8sia1, Tgfb2, Thbs4, Timp1, Tnc, Tnfsf18, Tnmd, Twist1, Wnk2, Wnt2, Zbtb16]
GO:0042326	negative regulation of phosphorylation	20	5,1813474	6,20E-04	[Angpt1, Drd1, Dusp7, Dynll1, Enpp1, Hspb1, Hsph1, Igf1, Inpp5j, Lif, Per1, Prnp, Rgn, Rgs2, Sfrp1, Sfrp2, Snca, Tbc1d10c, Twist1, Wnk2]
GO:0043069	negative regulation of programmed cell death	45	5,3956833	7,92E-07	[Adamts20, Angpt1, Arnt2, Bcl3, Cbs, Creb3l1, Crlf1, Cth, Cx3cl1, Cyr61, Dhcr24, Egfr, Egr2, Egr3, Erbb4, Faim2, Fn1, Foxc2, Herpud1, Hspa1b, Hspb1, Hsph1, Igf1, Mdk, Myc, Ngfr, Pik3r1, Pim3, Plac8, Plcg2, Pou4f1, Prnp, Rgn,

					Scx, Sfrp1, Sfrp2, Snai1, Snca, Sox9, Star, Tgfb2, Timp1, Tnfaip8, Tnfrsf23, Twist1]
GO:0043269	regulation of ion transport	34	5,5737705	1,52E-05	[Ace, Atp8a2, Cacnb1, Cacng6, Clcn1, Drd1, Edn3, Fhl1, Gck, Gnao1, Gpr39, Igf1, Itgb3, Kcnd2, Kcne1, Kcnh2, Kcnh7, Kcnj3, Kcnj6, Kcnv2, Nppa, Oprd1, Per1, Plcg2, Prnp, Ptgs2, Rgn, Rnf207, Shank1, Slc38a3, Snca, Tgfb2, Twist1, Wnk2]
GO:0043408	regulation of MAPK cascade	31	5,175292	1,17E-04	[Angpt1, Cbs, Ctgf, Cyr61, Dixdc1, Dusp7, Edn3, Egfr, Erbb4, Ereg, Fgf18, Gdf15, Gdf6, Grm4, Hsph1, Igf1, Itgb3, Lepr, Lif, Lpar2, Mdfi, Myoc, Ngfr, Per1, Pla2g5, Rgs2, Sfrp1, Sfrp2, Tbc1d10c, Tgfb2, Wnk2]
GO:0044057	regulation of system process	27	6,1085973	3,69E-05	[Corin, Cry2, Ctgf, Cx3cl1, Drd1, Dsg2, Edn3, Egfr, Gnao1, Gpr39, Igf1, Kcne1, Kcnh2, Lif, Lmcd1, Mmp2, Ngfr, Nppa, Nppb, Oprd1, Pi16, Pik3r1, Ptgs2, Rgs2, Rnf207, Runx1, Tgfb2]
GO:0045596	negative regulation of cell differentiation	36	5,106383	4,69E-05	[Arntl, Bex1, Col3a1, Col5a1, Col5a2, Corin, Ctla4, Dixdc1, Dpysl3, Enpp1, Ereg, Foxc2, Fst, Fstl3, Igf1, Inpp5j, Itgb3, Kctd11, Leo1, Lif, Myc, Ngef, Ngfr, Padi4, Pi16, Pik3r1, Pthlh, Runx1, Sfrp1, Sfrp2, Snai1, Sox9, Tgfb2, Tob2, Twist1, Zbtb16]
GO:0045597	positive regulation of cell differentiation	47	5,452436	3,00E-07	[Ace, Adamts20, Ankrd1, Arntl, Atp8a2, Bex1, Cd276, Col1a1, Ctgf, Cthrc1, Cx3cl1, Cyr61, Dixdc1, Dpysl3, Edn3, Egr3, Fbn2, Fgf18, Fn1, Gdf15, Gdf6, Igf1, Itgb3, Kctd11, Lif, Loxl3, Lrp8, Myoc, Neurl1a, Pik3r1, Ptgs2, Ptn, Runx1, Serpinf1, Sfrp1, Sfrp2, Sh3pxd2b, Shank1, Snai1, Sox9, Star, Tgfb2, Tnfrsf12a, Twist1, Vwc2, Wnt5b, Zbtb16]
GO:0045785	positive regulation of cell adhesion	24	7,594937	3,88E-06	[Angpt1, Ccdc80, Ccl2, Cd276, Cd4, Col16a1, Col26a1, Col8a1, Cx3cl1, Cyr61, Egflam, Egr3, Emilin1, Foxc2, Fstl3, Hsph1, Igf1, Igfbp2, Itgb3, Myoc, Ptn, Tgfb2, Vwc2, Zbtb16]
GO:0045936	negative regulation of phosphate metabolic process	29	5,6530213	5,39E-05	[Angpt1, Cda, Cry2, Csrnp3, Drd1, Dusp7, Dynll1, Enpp1, Fbp2, Hspb1, Hsph1, Igf1, Inpp5j, Lif, Pcdh11x, Pdzd3, Per1, Prnp, Rgn, Rgs2, Sfrp1, Sfrp2, Sh2d4a, Slc27a1, Snca, Tbc1d10c, Tgfb2, Twist1, Wnk2]
GO:0048514	blood vessel morphogenesis	38	7,5247526	1,72E-09	[Ace, Amot, Angpt1, Ccl11, Ccl2, Col3a1, Col4a1, Col8a1, Col8a2, Ctgf, Cx3cl1, Cyp1b1, Cyr61, Ecm1, Egr3, Ereg, Esm1, Fgf18, Fgf6, Fn1, Foxc2, Hif3a, Hspb1, Itgb3, Lepr, Lif, Loxl3, Mmp2, Otulin, Prrx2, Ptgs2, Runx1, Serpinf1, Sfrp2, Sparc, Srpx2, Tnfrsf12a, Tnmd]
GO:0048608	reproductive structure development	23	5,6930695	2,97E-04	[Angpt1, Cyr61, Dhcr24, Egfr, Ereg, Fgf7, Fst, Igf1, Lif, Mdfi, Mmp2, Nr5a1, Nupr1, Ptgs2, Runx1, Serpinf1, Sfrp1, Sfrp2, Snai1, Sox9, St14, Tnc, Wnt2]
GO:0048646	anatomical structure formation involved in morphogenesis	69	6,1883407	2,64E-13	[Ace, Acta1, Amot, Angpt1, Ankrd23, Atp8a2, Bcl3, Ccl11, Ccl2, Celsr3, Col1a1, Col4a1, Col5a1, Col5a2, Col8a1, Col8a2, Ctgf, Cthrc1, Cx3cl1, Cyp1b1, Cyr61, Ecm1, Egr2, Egr3, Enah, Ereg, Esm1, Faim2, Fbn2, Fgf18, Fgf6, Fn1, Foxc2, Gdf15, Hif3a, Hspb1, Itgb3, Leo1, Lepr, Lif, Loxl3, Lrp8, Meox1, Mfap2, Mmp2, Neurl1a, Otulin, Ptgs2, Pthlh, Pvrl1, Rp1, Runx1, Sbno2, Scx, Serpinf1, Sfrp1, Sfrp2, Snai1, Sox9, Sparc, Srpx2, St14, T2, Tcap, Tnfrsf12a, Tnmd, Ttll1, Twist1, Wnt2]

GO:0048705	skeletal system morphogenesis	23	10,043668	5,72E-08	[Acan, Cbs, Col11a1, Col1a1, Ctgf, Fbn2, Fgf18, Fgf6, Foxc2, Frem1, Mdfi, Mmp14, Mmp2, Myc, Prrx2, Pthlh, Scx, Sfrp1, Sfrp2, Sox9, Tbx15, Tgfb2, Twist1]
GO:0048729	tissue morphogenesis	42	6,521739	1,30E-08	[Aldh1a2, Angpt1, Ankrd1, Atp8a2, Ccl11, Col11a1, Col3a1, Col4a1, Col5a1, Cthrc1, Cyr61, Egfr, Enah, Etv4, Fgf7, Foxc2, Fst, Gcnt4, Igf1, Lif, Mgp, Mmp14, Mmp2, Myc, Ngfr, Pou4f1, Pthlh, Ptn, Rp1, Runx1, Scx, Sfrp1, Sfrp2, Snai1, Sox9, St14, Tcap, Tgfb2, Tnc, Twist1, Wnt2, Xirp2]
GO:0048870	cell motility	67	5,6876063	2,96E-11	[Acan, Ace, Amot, Angpt1, Ccl11, Ccl2, Ccl21a, Celsr3, Col1a1, Col3a1, Col5a1, Ctgf, Cthrc1, Cx3cl1, Cyp1b1, Cyr61, Dixdc1, Dpysl3, Drd1, Ecm1, Edn3, Efhc1, Egfr, Egr3, Erbb4, Fgf18, Fgf7, Fn1, Foxc2, Has1, Hspb1, Igf1, Itga11, Itga9, Itgb3, Loxl3, Lrp8, Lrrc15, Mdk, Mmp14, Mmp2, Mmp3, Myoc, Neurl1a, Pik3r1, Plvap, Pou4f1, Ptgs2, Rgn, Rras2, Sdc1, Serpinf1, Sfrp1, Sfrp2, Snai1, Sorbs2, Sox9, Sparc, Srgap3, Srpx2, St14, Tgfb2, Thbs4, Timp1, Tnfrsf12a, Twist1, Wnt5b]
GO:0050673	epithelial cell proliferation	33	9,295774	1,40E-10	[Aldh1a2, Ccl11, Ccl2, Col8a1, Col8a2, Ecm1, Egfr, Egr3, Erbb4, Ereg, Etv4, Fabp7, Fgf7, Fst, Igf1, Itgb3, Klf9, Loxl3, Myc, Nr1d1, Ptn, Ptprv, Rgn, Serpinf1, Sfrp1, Sfrp2, Sox9, Sparc, Tgfb2, Thbs4, Tnmd, Twist1, Wnt2]
GO:0050678	regulation of epithelial cell proliferation	26	8,934708	5,85E-08	[Aldh1a2, Ccl11, Ccl2, Ecm1, Egfr, Egr3, Erbb4, Etv4, Fgf7, Igf1, Itgb3, Klf9, Myc, Nr1d1, Ptn, Rgn, Serpinf1, Sfrp1, Sfrp2, Sox9, Sparc, Tgfb2, Thbs4, Tnmd, Twist1, Wnt2]
GO:0051093	negative regulation of developmental process	49	5,4384017	1,59E-07	[Amot, Arntl, Bex1, Ccl2, Col3a1, Col5a1, Col5a2, Corin, Ctla4, Dixdc1, Dpysl3, Ecm1, Enpp1, Ereg, Etv4, Foxc2, Fst, Fstl3, Igf1, Inpp5j, Itgb3, Kctd11, Leo1, Lif, Myc, Ngef, Ngfr, Nr5a1, Padi4, Pi16, Pik3r1, Plac8, Pthlh, Rgn, Runx1, Serpinf1, Sfrp1, Sfrp2, Snai1, Sox9, Sparc, Tgfb2, Timp1, Tnfrsf11b, Tnmd, Tob2, Twist1, Usp2, Zbtb16]
GO:0051094	positive regulation of developmental process	67	5,6208053	4,92E-11	[Ace, Adamts20, Amot, Ankrd1, Arntl, Atp8a2, Bex1, Ccl11, Cd276, Col1a1, Ctgf, Cthrc1, Cx3cl1, Cyp1b1, Cyr61, Dixdc1, Dpysl3, Ecm1, Edn3, Egr3, Erbb4, Fbn2, Fgf18, Fgf7, Fn1, Foxc2, Foxs1, Fst, Gdf15, Gdf6, Hspb1, Igf1, Itgb3, Kctd11, Lif, Loxl3, Lrp8, Lrrn1, Myc, Myoc, Neurl1a, Ngfr, Nr5a1, Pik3r1, Ptgs2, Ptn, Runx1, Scx, Serpinf1, Sfrp1, Sfrp2, Sh3pxd2b, Shank1, Slitrk2, Snai1, Sox9, Srpx2, Star, Syndig1, Tgfb2, Tnfrsf12a, Twist1, Usp2, Vwc2, Wnt2, Wnt5b, Zbtb16]
GO:0051239	regulation of multicellular organismal process	128	5,1097803	5,59E-19	[Ace, Adamts20, Afap1l2, Amot, Angpt1, Ankrd1, Aqp4, Arntl, Atp8a2, Bcl3, Bex1, Ccl11, Ccl2, Cd276, Cenpf, Col1a1, Col3a1, Col5a1, Col5a2, Colq, Corin, Creb3l1, Cry2, Ctgf, Cthrc1, Ctla4, Cx3cl1, Cyp1b1, Cyr61, Dixdc1, Dpysl3, Drd1, Dsg2, Ecm1, Edn3, Egfr, Egr2, Egr3, Enpp1, Erbb4, Ereg, Etv4, Fbn2, Fgf18, Fgf7, Fn1, Foxc2, Foxs1, Fst, Fstl3, Gdf6, Gnao1, Gpr39, Hspb1, Igf1, Inpp5j, Itgb3, Kcne1, Kcnh2, Kctd11, Lag3, Leo1, Lif, Lmcd1, Loxl3, Lrp8, Lrrn1, Mfap4, Mgp, Mmp2, Myc, Neurl1a, Ngef, Ngfr, Nlrc3, Nppa, Nppb, Nr1d2, Nr5a1, Nupr1, Oprd1, Panx1, Per1, Per3, Pi16, Pik3r1, Plac8, Pou4f1, Prnp, Ptgds, Ptgs2, Pthlh, Ptn, Pvrl1, Rbp1, Rgn, Rgs2, Rnf207, Runx1, Scx, Serpinf1, Sfrp1, Sfrp2, Shank1, Slc27a1, Slitrk2, Snai1, Sox9, Sparc, Spon2, Srpx2, Ssc5d, Star, Syndig1, Tg, Tgfb2, Thbs4, Timp1, Tnfrsf11b, Tnfrsf12a, Tnmd, Tob2, Tril, Twist1, Usp2, Vwc2, Wnt2, Zbtb16]

GO:0051240	positive regulation of multicellular organismal process	76	5,3184047	2,06E-11	[Ace, Afap1l2, Amot, Angpt1, Ankrd1, Arntl, Atp8a2, Bcl3, Bex1, Ccl11, Ccl2, Cd276, Col1a1, Ctgf, Cthrc1, Cx3cl1, Cyp1b1, Cyr61, Dixdc1, Dpysl3, Ecm1, Edn3, Egfr, Egr3, Erbb4, Ereg, Fbn2, Fgf18, Fgf7, Fn1, Foxc2, Foxs1, Fst, Gdf6, Gpr39, Hspb1, Igf1, Itgb3, Kctd11, Lif, Loxl3, Lrp8, Lrrn1, Myc, Neurl1a, Ngfr, Nppa, Nppb, Nr5a1, Panx1, Pik3r1, Ptgs2, Ptn, Rgs2, Runx1, Scx, Serpinf1, Sfrp2, Shank1, Slc27a1, Slitrk2, Snai1, Sox9, Sparc, Spon2, Srpx2, Star, Syndig1, Tgfb2, Tnfrsf12a, Tob2, Twist1, Usp2, Vwc2, Wnt2, Zbtb16]
GO:0051241	negative regulation of multicellular organismal process	61	6,1	1,97E-11	[Amot, Angpt1, Aqp4, Bcl3, Bex1, Ccl2, Cd276, Col3a1, Col5a1, Col5a2, Corin, Cry2, Ctla4, Cx3cl1, Dixdc1, Dpysl3, Drd1, Ecm1, Enpp1, Etv4, Foxc2, Fstl3, Gpr39, Igf1, Inpp5j, Kctd11, Lag3, Leo1, Lif, Mmp2, Myc, Ngef, Ngfr, Nlrc3, Nppa, Nr5a1, Pi16, Pik3r1, Plac8, Prnp, Ptgds, Ptgs2, Pthlh, Rgn, Rgs2, Runx1, Serpinf1, Sfrp1, Sfrp2, Snai1, Sox9, Sparc, Ssc5d, Tgfb2, Timp1, Tnfrsf11b, Tnmd, Tob2, Twist1, Usp2, Zbtb16]
GO:0051270	regulation of cellular component movement	52	7,355021	1,10E-12	[Acan, Ace, Amot, Angpt1, Ccl11, Ccl2, Ccl21a, Col1a1, Col3a1, Cx3cl1, Cyp1b1, Cyr61, Dpysl3, Drd1, Dsg2, Ecm1, Edn3, Egfr, Erbb4, Fgf18, Fgf7, Fn1, Foxc2, Has1, Hspb1, Igf1, Itgb3, Kcnh2, Lrrc15, Mmp14, Mmp2, Mmp3, Myoc, Pik3r1, Plvap, Ptgs2, Rgn, Rnf207, Rras2, Serpinf1, Sfrp1, Sfrp2, Snai1, Sox9, Sparc, Srgap3, Srpx2, Tgfb2, Thbs4, Timp1, Twist1, Wnt5b]
GO:0051347	positive regulation of transferase activity	23	5	9,48E-04	[Ace, Afap1l2, Angpt1, Cd4, Cyr61, Edn3, Egfr, Ereg, Fgf18, Grm4, Hsph1, Igf1, Itgb3, Lpar2, Lrp8, Mdfi, Neurl1a, Pdgfc, Pfkfb1, Serinc2, Slc27a1, Snca, Tgfb2]
GO:0051962	positive regulation of nervous system development	25	5,0916495	5,31E-04	[Ace, Ankrd1, Atp8a2, Bex1, Cx3cl1, Dixdc1, Dpysl3, Fn1, Gdf6, Igf1, Kctd11, Lif, Lrp8, Lrrn1, Neurl1a, Ngfr, Ptn, Serpinf1, Shank1, Slitrk2, Srpx2, Star, Syndig1, Tnfrsf12a, Vwc2]
GO:0060537	muscle tissue development	29	7,323232	5,20E-07	[Acta1, Aldh1a2, Angpt1, Ankrd1, Arntl, Cenpf, Col11a1, Col3a1, Dsg2, Egr2, Eln, Erbb4, Foxc2, Gpcpd1, Hlf, Myc, Nr1d2, Nupr1, Pi16, Pou4f1, Rcan1, Scx, Sox9, Tcap, Tgfb2, Twist1, Usp2, Wnt2, Xirp2]
GO:0060548	negative regulation of cell death	51	5,610561	2,92E-08	[Adamts20, Angpt1, Arnt2, Bcl3, Cbs, Creb3l1, Crlf1, Ctgf, Cth, Cx3cl1, Cyr61, Dhcr24, Egfr, Egr2, Egr3, Erbb4, Faim2, Fn1, Foxc2, Herpud1, Hspa1b, Hspb1, Hsph1, Igf1, Itgb3, Mdk, Myc, Ngfr, Npas2, Npc1, Pik3r1, Pim3, Plac8, Plcg2, Pou4f1, Prnp, Pycr1, Rgn, Scx, Serpinf1, Sfrp1, Sfrp2, Snai1, Snca, Sox9, Star, Tgfb2, Timp1, Tnfaip8, Tnfrsf23, Twist1]
GO:0061061	muscle structure development	36	6,060606	1,21E-06	[Acta1, Angpt1, Ankrd1, Ankrd23, Arntl, Cenpf, Col11a1, Col3a1, Des, Egr2, Eln, Erbb4, Ereg, Fgf6, Foxc2, Gdf15, Gpcpd1, Hlf, Igf1, Lif, Mir208b, Myc, Nr1d2, Nupr1, Pi16, Pik3r1, Pou4f1, Rcan1, Scx, Sdc1, Sox9, Tcap, Twist1, Usp2, Wnt2, Xirp2]
GO:0061448	connective tissue development	24	10,572687	9,48E-09	[Acan, Cbs, Col11a1, Col1a1, Col5a1, Ctgf, Cyr61, Dgat2, Fgf18, Fgf6, Foxc2, Igf1, Itgb3, Loxl3, Mgp, Prrx2, Pthlh, Scx, Sfrp2, Sh3pxd2b, Snai1, Sox9, Tgfb2, Zbtb16]
GO:0070838	divalent metal ion transport	21	5,159705	7,02E-04	[Ace, Cacnb1, Cacng6, Ctgf, Drd1, Gnao1, Gpr39, Igf1, Itgb3, Kcne1, Nppa, Oprd1, Orai2, Panx1, Plcg2, Ptgs2, Rgn, Slc39a8, Slc8a2, Snca, Tgfb2]

GO:0071345	cellular response to cytokine stimulus	21	5,0119333	3,45E-04	[Angpt1, Ankrd1, Aqp4, Ccl2, Ccrl2, Cx3cl1, Cxcr6, Ecm1, Ereg, Fn1, Lepr, Nfil3, Plvap, Ptprn, Rps6ka5, Sfrp1, Sh2b2, Slc26a6, Slc27a1, Star, Tnfsf18]
GO:0071363	cellular response to growth factor stimulus	25	6,4267354	3,79E-05	[Adamts3, Adamtsl2, Angpt1, Ankrd1, Bex1, Ccl2, Col1a2, Col3a1, Ctgf, Dok5, Egfr, Egr3, Fbn1, Fbn2, Fgf18, Fgf6, Fgf7, Has1, Hspb1, Ngfr, Runx1, Sfrp1, Sox9, Sparc, Tgfb2]
GO:0071417	cellular response to organonitrogen compound	28	6,8292685	3,46E-06	[Blk, Col16a1, Col1a1, Col1a2, Col3a1, Col4a1, Col5a2, Col6a1, Drd1, Egfr, Egr2, Egr3, Enpp1, Foxc2, Gck, Irs3, Mmp2, Mmp3, Neurl1a, Ngfr, Pdgfc, Pik3r1, Ptprv, Sfrp1, Sh2b2, Slc25a33, Slc26a6, Sox9]
GO:0071495	cellular response to endogenous stimulus	49	5,632184	5,61E-08	[Adamtsl2, Ankrd1, Blk, Ccl2, Col16a1, Col1a1, Col1a2, Col3a1, Col4a1, Col5a2, Col6a1, Ctgf, Drd1, Egfr, Egr2, Egr3, Enpp1, Fbn1, Fbn2, Fgf18, Fgf6, Fgf7, Foxc2, Gck, Gpr22, Has1, Irs3, Klf9, Lepr, Mmp2, Mmp3, Neurl1a, Ngfr, Npc1, Nr1d1, Nr1d2, Nr3c2, Nr5a1, Pdgfc, Pik3r1, Ptprv, Runx1, Sfrp1, Sh2b2, Slc25a33, Slc26a6, Slc27a1, Sox9, Tgfb2]
GO:0072358	cardiovascular system development	62	6,8508286	7,81E-14	[Ace, Adam19, Aldh1a2, Amot, Angpt1, Ankrd1, Ccl11, Ccl2, Col11a1, Col1a1, Col1a2, Col3a1, Col4a1, Col5a1, Col8a1, Col8a2, Ctgf, Cx3cl1, Cyp1b1, Cyr61, Dsg2, Ecm1, Egr3, Erbb4, Ereg, Esm1, Fbn1, Fgf18, Fgf6, Fn1, Foxc2, Foxs1, Hif3a, Hspb1, Igf1, Itgb3, Lepr, Lif, Lox, Loxl3, Mmp2, Otulin, Pi16, Pou4f1, Prrx2, Ptgs2, Runx1, Scx, Serpinf1, Sfrp2, Sh3pxd2b, Snai1, Sox9, Sparc, Srpx2, Tcap, Tgfb2, Tnfrsf12a, Tnmd, Twist1, Wnt2, Xirp2]
GO:1901700	response to oxygen-containing compound	61	5,1217465	2,04E-08	[Ace, Adam19, Adh1, Aldob, Ankrd1, Aqp4, Blk, Cbs, Ccl2, Col16a1, Col1a1, Col1a2, Col3a1, Col4a1, Col5a2, Col6a1, Cry2, Cyp1b1, Dgat2, Drd1, Egfr, Egr2, Egr3, Enpp1, Foxc2, Gck, Gpr22, Gpr39, Hsph1, Irs3, Klf9, Mmp2, Mmp3, Neurl1a, Ngfr, Nlrc3, Nnat, Nr1d1, Panx1, Pdgfc, Per1, Pik3r1, Pim3, Plcg2, Ptgs2, Ptprn, Ptprv, Pycr1, Rgn, Runx1, Sfrp1, Sh2b2, Slc25a33, Slc26a6, Slc27a1, Snca, Sox9, Spon2, Tgfb2, Tnip3, Ucp3]
GO:1901701	cellular response to oxygen-containing compound	42	5,172414	5,88E-06	[Ankrd1, Aqp4, Blk, Ccl2, Col16a1, Col1a1, Col1a2, Col3a1, Col4a1, Col5a2, Col6a1, Cyp1b1, Dgat2, Drd1, Egfr, Egr2, Egr3, Enpp1, Foxc2, Gck, Gpr39, Hsph1, Irs3, Klf9, Mmp2, Mmp3, Neurl1a, Ngfr, Nr1d1, Pdgfc, Pik3r1, Pim3, Ptprv, Pycr1, Rgn, Sfrp1, Sh2b2, Slc25a33, Slc26a6, Sox9, Spon2, Tnip3]
GO:1902532	negative regulation of intracellular signal transduction	22	5,6847544	4,10E-04	[Arntl, Creb3l1, Dusp7, Fbp2, Herpud1, Hspb1, Hsph1, Igf1, Lif, Mmp3, Myoc, Nlrc3, Per1, Prnp, Rgs2, Sfrp1, Sfrp2, Snai1, Tbc1d10c, Tnip3, Twist1, Wnk2]
GO:2000026	regulation of multicellular organismal development	89	5,3102627	1,76E-13	[Ace, Adamts20, Amot, Ankrd1, Arntl, Atp8a2, Bex1, Ccl11, Ccl2, Cd276, Cenpf, Col1a1, Col3a1, Col5a1, Col5a2, Colq, Corin, Ctgf, Cthrc1, Ctla4, Cx3cl1, Cyp1b1, Cyr61, Dixdc1, Dpysl3, Ecm1, Egr3, Erbb4, Etv4, Fbn2, Fgf18, Fgf7, Fn1, Foxc2, Fst, Fstl3, Gdf6, Hspb1, Igf1, Inpp5j, Itgb3, Kctd11, Leo1, Lif, Loxl3, Lrp8, Lrrn1, Mgp, Myc, Neurl1a, Ngef, Ngfr, Nr1d2, Nr5a1, Nupr1, Pi16,

					Pik3r1, Pou4f1, Ptgs2, Pthlh, Ptn, Pvrl1, Rbp1, Rgn, Runx1, Scx, Serpinf1, Sfrp1, Sfrp2, Shank1, Slitrk2, Snai1, Sox9, Sparc, Srpx2, Star, Syndig1, Tg, Tgfb2, Timp1, Tnfrsf11b, Tnfrsf12a, Tnmd, Tob2, Twist1, Usp2, Vwc2, Wnt2, Zbtb16]
GO:2000147	positive regulation of cell motility	37	10,081744	6,50E-13	[Amot, Angpt1, Ccl11, Ccl2, Ccl21a, Col1a1, Cx3cl1, Cyp1b1, Cyr61, Drd1, Edn3, Egfr, Erbb4, Fgf18, Fgf7, Fn1, Foxc2, Hspb1, Igf1, Itgb3, Lrrc15, Mmp14, Mmp2, Mmp3, Myoc, Pik3r1, Plvap, Ptgs2, Rras2, Snai1, Sox9, Sparc, Srpx2, Tgfb2, Thbs4, Twist1, Wnt5b]
REACTOME:5991414	Extracellular matrix organization	46	18,93004	6,66E-28	[Adamts3, Adamts4, Bgn, Col11a1, Col15a1, Col16a1, Col1a1, Col1a2, Col22a1, Col26a1, Col3a1, Col4a1, Col4a4, Col5a1, Col5a2, Col5a3, Col6a1, Col6a2, Col6a3, Col8a1, Col8a2, Col9a2, Ctsk, Eln, Fbn1, Fbn2, Fn1, Itga11, Itga9, Itgb3, Lamc3, Loxl1, Mfap4, Mfap5, Mmp14, Mmp2, Mmp3, P3h2, Pcolce, Sdc1, Sparc, Tgfb2, Timp1, Tll2, Tnc, Tpsb2]
REACTOME:5992182	Collagen formation	25	35,714287	3,08E-22	[Adamts3, Col11a1, Col15a1, Col16a1, Col1a1, Col1a2, Col22a1, Col26a1, Col3a1, Col4a1, Col4a4, Col5a1, Col5a2, Col5a3, Col6a1, Col6a2, Col6a3, Col8a1, Col8a2, Col9a2, Loxl1, Mmp3, P3h2, Pcolce, Tll2]
REACTOME:5992212	Collagen biosynthesis and modifying enzymes	22	39,285713	1,43E-20	[Adamts3, Col11a1, Col15a1, Col16a1, Col1a1, Col1a2, Col22a1, Col26a1, Col3a1, Col4a1, Col4a4, Col5a1, Col5a2, Col5a3, Col6a1, Col6a2, Col6a3, Col8a1, Col8a2, Col9a2, P3h2, Pcolce]

Supplemental Table 3: Top 100 differentially regulated genes in the transcriptomes of D2-TAC (n=3) vs. D2-shunt mice (n=5).

gene name	baseMean	log2FoldChange	padj
Syndig1	110	-3,54	4,81E-34
Ankrd1	73432	-2,64	5,92E-44
Rcan1	7109	-2,60	4,15E-39
Crlf1	187	-2,57	2,72E-14
Adamts4	116	-2,55	2,08E-13
Egr2	90	-2,47	2,70E-15
Tgfb2	816	-2,15	6,63E-23
Prrx2	29	-2,14	1,60E-11
Frem1	103	-2,12	1,08E-10
Foxs1	186	-2,09	5,80E-18
Npas2	185	-2,03	6,32E-13
Nlrc3	236	-1,93	7,29E-12
Srpx	183	-1,92	1,29E-13
Nfil3	815	-1,85	9,78E-34
Col1a1	12542	-1,80	3,88E-10
Xirp2	34562	-1,75	5,51E-18
Fhl1	16571	-1,72	2,51E-10
Sh2d4a	470	-1,71	3,04E-12
Cpxm1	362	-1,70	7,17E-19
Mmp14	889	-1,65	3,51E-12
Igf2bp2	166	-1,63	2,29E-15
Adam19	1489	-1,62	3,28E-13
Lhfpl2	408	-1,59	2,24E-13
Ankrd23	20717	-1,54	1,78E-11
Hspb1	2073	-1,54	4,09E-23
Ckap4	2009	-1,51	5,85E-13
Creb3l1	281	-1,48	4,91E-13
Fam198b	3049	-1,47	1,12E-22
Hsph1	1758	-1,44	8,98E-19
Enah	6197	-1,44	7,83E-17
Cyr61	1951	-1,41	2,27E-10
Uck2	1001	-1,37	3,63E-10
Lmcd1	1490	-1,37	2,81E-15
P4ha1	2373	-1,35	1,26E-19

Ccdc136	178	-1,34	2,54E-10
Bace2	299	-1,31	7,27E-14
Atp8a2	336	-1,29	4,39E-10
Dynll1	1167	-1,26	6,23E-10
Igfbp6	459	-1,20	3,77E-10
Dpysl3	4978	-1,18	2,94E-14
Mmp2	4785	-1,18	4,23E-10
Tspan9	4893	-1,17	1,29E-11
Sorbs2	21154	-1,14	1,31E-15
Vwa1	783	-1,10	1,36E-10
Rasl11b	1760	-1,07	9,43E-12
Rras2	2098	-1,07	8,84E-18
Prnp	6810	-1,07	3,84E-12
Inpp5j	1120	-1,06	2,04E-20
Des	81633	-1,00	1,45E-11
Egflam	824	1,03	1,64E-16
Fam214a	889	1,03	4,83E-19
Cacng6	415	1,04	9,94E-11
Dsg2	2199	1,05	1,01E-12
Ppat	1221	1,05	7,47E-20
Abcd2	396	1,05	3,62E-10
Dusp7	1412	1,06	2,99E-10
Gm16793	188	1,06	6,33E-10
Slc26a6	448	1,07	4,54E-10
Kcnd2	1080	1,11	1,16E-10
Emilin2	713	1,11	1,75E-13
Ccrl2	361	1,12	2,85E-11
9030617O03Rik	1318	1,15	2,34E-23
Nr3c2	1369	1,17	2,81E-15
Klf9	3199	1,18	3,36E-14
Pla2g5	997	1,19	1,04E-21
Slc27a1	4585	1,22	8,66E-19
Pdp2	553	1,25	7,06E-13
Gpt2	2050	1,26	6,92E-21
Ttll1	2360	1,26	4,31E-14
Ppp1r3a	6765	1,26	1,04E-10
Kcnj3	1967	1,26	4,07E-10
Sned1	311	1,29	2,21E-12
Adamts3	291	1,31	3,64E-10
Stard3	1202	1,32	3,46E-24
Art5	876	1,32	3,15E-11

Tnfaip8	1380	1,33	1,37E-14
Rgs2	1660	1,35	8,60E-13
Pik3r1	5955	1,39	3,89E-14
Gpcpd1	7375	1,45	3,76E-27
Lamb3	540	1,46	1,52E-14
Cry2	1217	1,48	7,83E-16
Npc1	2678	1,51	4,32E-62
Tcap	55452	1,51	2,23E-12
A930018M24Rik	489	1,55	1,06E-17
Mettl20	607	1,55	1,52E-11
Mir208b	99	1,58	2,38E-10
Usp2	4454	1,65	1,16E-13
1110034G24Rik	1259	1,72	6,05E-21
Rasd2	224	1,75	1,78E-11
Pfkfb1	134	1,81	1,16E-15
Aqp4	199	1,84	2,29E-17
Clcn1	201	1,88	2,22E-10
Slc16a7	590	1,88	6,46E-21
Tef	5424	1,90	1,88E-14
Lgals4	105	1,93	2,59E-16
Klhl33	416	2,07	1,34E-24
Hlf	1334	2,12	3,11E-16
Fbp2	265	2,15	5,24E-26
Nr1d2	3882	2,25	6,36E-36
Dbp	2624	3,75	3,36E-47