

Supplemental table 4A. Top Biological Functions affected by E2: Diseases and disorders

Biological Function	Molecules in Network	p-value	# of molecules
Cancer	ABCC5, AFP, ALDH1A2, ALDH1A3, ANGPT2, ANGPTL4, ANXA2, BNIPL, C3, C7ORF68, C8ORF84, CAPG, CAV1, CCL19, CCL21, CD177, CDK3, CFB, CFD, CLDN4, CLEC10A, CREB3L3, CXCL2, DCN, DLGAP1, DMPK, DNAJA1, DTNA, EHHADH, EMP1, EPHA2, ETV1, F3, FABP4, FLT3LG, FOSL1, FTL, GCH1, GDF15, GHRL, GPRC5A, GRP, HNMT, HSD17B6, HSD17B11, HSPA1A, IER3, IGF2, IL33, IL17B, IL1A, INHBA, ITGA2, ITIH5, ITLN1, KIAA1199, KRT20, LAMA3, LAMC2, LOX, MGP, MMP3, MMP10, MMP13, MYB (includes EG:4602), MYH11, NGFR, NOS1, NUPR1, PCP4, PDLIM3, PHLDA2, PIK3R1, PIPOX, PLA2G2A, PLAUR, PLEKHB1, PLIN2, POPDC2, PPL, PPP2R2B, PRL, PRNP, PTN, RBM4B, RELN, RETNLA, RGS2, RGS5, RTN1, SCG5, SDPR, SECTM1, SERPINE1, SFRP2, SFRP4, SLC1A4, SLC7A11, SMARCD3, SNCG, SPARCL1, SPHK1, STC1, STMN3, SYNPO2, TAGLN, TCF21, TNFRSF10A (includes EG:8797), TNS1, TNXB, TPM2, TRO, UCHL1, VTCN1, VWF	4.41E-07 - 2.18E-02	115
Reproductive System Disease	ABCC5, AFP, ALDH1A2, ALDH1A3, ANGPT2, ANXA2, APOBEC3B, BNIPL, C3, C7ORF68, C8ORF84, CAV1, CCL19, CCL21, CFB, CLDN4, CLEC10A, DCN, DLGAP1, DTNA, EPHA2, ETV1, F3, FABP4, FOSL1, GDF15, GHRL, GPRC5A, HSD17B6, IER3, IL1A, INHBA, ITLN1, KIAA1199, MGP, MMP3, NOS1, PENK, PIK3R1, PLAUR, PLEKHB1, PRL, RBM4B, SERPINE1, SFRP4, SLC1A4, SMARCD3, STC1, TNXB, TRO, UCHL1, VTCN1	3.82E-04 - 2.18E-02	52
Cardiovascular Disease	ABCC5, ABCG5, ADAMTS12, AMICA1, ANGPT2, ANGPTL4, ANO10, ANXA2, APOC2, ASB13, BGLAP, BMPER, C3, C9ORF71, CAMK2G, CARTPT, CAV1, CDK14, CFB, COLEC10, DES, DIO2, DTNA, F3, FABP4, FGD3, FLT3LG, FOSL1, FXYD6, GDF15, GHRL, HMP19, HNMT, IGF2, IL33, IL1A, ITGA2, ITIH5, ITPR2, KIAA1199, LIMS2, LTBP2, MAMDC2, MCF2L, MEIS2, MGP, MMP3, MYH11, MYLK, NGFR, NOS1, NTF4, PHACTR1, PLA2G5, PLA2G2A, PLEKHB1, PON2, PPL, PPP1R12B, PRL, PRNP, PRODH, RELN, RGS2, RGS5, RIMS1, SCNN1A, SERPINE1, SLC1A4, SNTG2, SYNPO2, SYT1, TNS1, TTC9, UTS2, VIP, VWF, WDR72, XDH	4.73E-04 - 2.18E-02	79
Organismal Injury and Abnormalities	ANGPT2, ANXA2, CAV1, F3, INHBA, ITGA2, LIMS2, NGFR, PLA2G2A, PRNP, SCNN1A, SERPINE1, SERPINI1, SPHK1, UTS2, VWF	4.73E-04 - 2.18E-02	16
Genetic Disorder	ABCG5, ALDH1A2, ALDH1A3, ANGPTL4, ANXA2, C3, CARTPT, CAV1, CFB, CHGB, CIDEA, CLDN5, CPE, DCN, DLGAP1, DTNA, ELAVL4, ETV1, FABP4, FLNB, FTL, FXYD1, FXYD6, GCH1, GDF15, GHRL, GPRC5A, HMGCS2, HSD17B6, IER3, IL1A, KIF5A, LAMA3, LAMC2, MMP13, MYH11, NGFR, NOS1, NPY, NTF4, PCP4, PIK3R1, PLAUR, PLEKHB1, PMM1, PRG4 (includes EG:10216), PRL, PRNP, PRODH, RELN, RTN1, SCG5, SERPINE1, SERPINI1, SLC1A4, SLC7A11, SMARCD3, SYT1, TNXB, UCHL1, XDH	5.30E-04 - 2.18E-02	61

Supplemental table 4B. Top Biological Functions affected by E2: Molecular and Cellular functions

Biological Function	Molecules in Network	p-value	# of molecules
Cellular Movement	ABHD2, ANGPT2, ANGPTL4, ANXA2, C3, CARTPT, CAV1, CCL19, CCL21, CFB, CLDN4, CXCL2, CXCL15, DCN, DNAJA1, EPHA2, ETV1, F3, FABP4, FLNB, FLT3LG, FOSL1, GDF15, GHRL, GRP, IGF2, IGFBP6, IL33, IL1A, INHBA, ITGA2, LAMA3, LAMC2, LIMS2, LOX, LTBP2, MCF2L, MGP, MMP3, MMP10, MMP13, MYH11, MYLK, NGFR, NPY, NTF4, PARD6B, PENK, PIK3R1, PLA2G5, PLAUR, PON2, PRAP1, PRL, PRNP, PTN, RELN, RETNLA, SERPINE1, SFRP2, SFRP4, SNCG, SPHK1, STC1, STMN3, SYNM, TAGLN, TNFRSF10A (includes EG:8797), TNS1, UTS2, VIP, VTCN1, VWF, XDH	3.91E-09 - 2.02E-02	74
Cellular Development	ABCC5, ALDH1A2, ANGPTL4, ANXA2, BGLAP, BMPER, BNIPL, BVES, CAPG, CARTPT, CAV1, CCDC92 (includes EG:80212), CCL19, CDO1, CHRDL1, CXCL2, CXCL15, DCN, DES, DIO2, EPHA2, ERO1L, FABP4, FLT3LG, FOSL1, FTL, GDF15, GHRL, GRP, HSPA1A, IER3, IFI16, IGF2, IGFBP6, IL33, IL17B, IL1A, INHBA, ITGA2, IVL, LAMA3, LOX, MGP, MMP3, MMP13, MYB (includes EG:4602), MYH11, MYLK, NGFR, NTF4, PENK, PIGA, PIK3R1, PLAUR, PRG4 (includes EG:10216), PRL, PRNP, PTN, RELN, RETNLA, RGS2, SEC14L2, SERPINE1, SFRP2, SFRP4, SLC7A11, SMARCD3, SNCG, SPHK1, STC1, TCF21, TCF23, TRIM25, UCHL1, UTS2, VIP, XDH	7.48E-06 - 2.18E-02	77
Cell-To-Cell Signaling and Interaction	AFP, AMICA1, ANGPT2, ANXA2, C3, CARTPT, CAV1, CCL19, CCL21, CD177, CLDN4, CLDN5, CLEC10A, CXCL2, DCN, EPHA2, F3, FGD3, FLT3LG, GHRL, GRP, HS3ST1, IFI16, IGF2, IL33, IL1A, INHBA, ITGA2, ITLN1, LAMA3, LOX, MMP13, NGFR, NPY, NTF4, PARD6B, PENK, PIK3R1, PLA2G2A, PLAUR, PRL, PRNP, PTN, RELN, RETNLA, SERPINE1, STC1, TNFRSF10A (includes EG:8797), TNS1, VIP, VTCN1, VWF, XDH	8.25E-06 - 2.18E-02	53
Lipid Metabolism	ABCG5, ADH7, AFP, ALDH1A2, ALDH1A3, ANGPT2, ANGPTL4, ANXA2, APOC2, C3, CARTPT, CAV1, CFD, CIDEA, CPE, DNAJA1, DNAJB1, EHHADH, FABP4, GHRL, GREM2, GRP, IGF2, IL33, IL1A, INHBA, NGFR, NPY, OSTALPHA, PIK3R1, PLA2G5, PLA2G2A, PLCH2, PLIN2, PNLIPRP2, PON2, PRL, PRNP, RGS2, SCG5, SCNN1A, SEC14L2, SERPINE1, SPHK1, ST3GAL6, ST8SIA6, STC1, THRSP, TNXB, VIP, XDH	3.42E-05 - 2.18E-02	51
Molecular Transport	ABCG5, AFP, ANGPT2, ANGPTL4, ANXA2, C3, CAMK2G, CARTPT, CAV1, CCL19, CCL21, CFD, CIDEA, CPE, DCN, DIO2, DNAJB1, FABP4, FXYP1, GCH1, GHRL, GRP, IGF2, IL33, IL1A, INHBA, ITGA2, ITPR2, KRT20, LTBP2, MYB (includes EG:4602), NGFR, NOS1, NPY, OSTALPHA, PIK3R1, PLA2G5, PLA2G2A, PLAUR, PLIN2, PON2, PRL, PRNP, RGS2, SCG5, SCNN1A, SEC14L2, SERPINE1, SLC11A2, SPHK1, STC1, SYT1, UTS2, VIP, XDH	3.42E-05 - 2.18E-02	55

Supplemental table 4C. Top Biological Functions affected by E2: Physiological System and Development and Function

Biological Function	Molecules in Network	p-value	# of molecules
Behavior	ARC, CARTPT, CCL21, GCH1, GHRL, GRP, HSPA1A, NGFR, NOS1, NPY, NTF4, PDYN, PENK, PLAUR, PRNP, RGS2, RIMS1, UCHL1	2.55E-05 - 1.90E-02	18
Organismal Development	ALDH1A2, ANGPT2, ANGPTL4, ANXA2, ATP1F1, C3, CARTPT, CAV1, EPHA2, F3, FABP4, FLNB, GCH1, GHRL, HSPA1A, IGF2, IGFBP6, IL17B, IL1A, INHBA, ITGA2, ITPR2, LOX, MEP1B, MMP3, MMP13, MYB (includes EG:4602), NOS1, NPY, NTF4, PIK3R1, PLAUR, PLCD3, PON2, PRL, RGS5, SCNN1A, SERPINE1, SPHK1, STC1, UTS2, VIP	4.52E-05 - 1.90E-02	42
Cardiovascular System Development and Function	ALDH1A2, ANGPT2, ANGPTL4, ANXA2, ATP1F1, C3, CARTPT, CAV1, CXCL15, DCN, DIO2, EMP1, EPHA2, F3, FABP4, GCH1, GHRL, GRP, IFI16, IGF2, IL17B, IL1A, INHBA, ITGA2, LOX, MGP, MMP3, MMP13, MYB (includes EG:4602), MYH11, NOS1, NPY, NUPR1, PIK3R1, PLAUR, PLCD3, PRL, PTN, RGS2, RGS5, SCNN1A, SERPINE1, SPHK1, STC1, UTS2, VIP, VWF	4.91E-05 - 1.90E-02	47
Embryonic Development	ALDH1A2, ALDH1A3, ANXA2, C3, CAV1, EPHA2, GRP, IGF2, INHBA, ITGA2, LIMS2, MYH11, NPNT, PIGA, PIK3R1, PLAUR, PRL, RELN, SFRP4, SPHK1, TCF21, TRO	9.18E-05 - 2.18E-02	22
Hair and Skin Development and Function	ANXA2, CAV1, HSPA1A, INHBA, PLAUR, RELN, SERPINE1	9.18E-05 - 8.86E-03	7

Supplemental table 4D. Top Canonical Pathways affected by E2

Canonical Pathway	p-value
LPS/IL-1 Mediated Inhibition of RXR Function	4.43E-03
Coagulation System	4.90E-03
Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis	5.90E-03
Aldosterone Signaling in Epithelial Cells	8.99E-03
Atherosclerosis Signaling	1.11E-02