

Supplementary Table 1. Pathways of changes in hypermethylation in F1 offspring exposed to intrauterine hyperglycemia

Pathway	Enrichment Score (-log ₁₀ [P value])	p-value	genes
Glycosaminoglycan degradation	2	0.006197	Hyal2;Hyal1
Fatty acid elongation in mitochondria	2	0.006197	Hadha;Echs1
Glycosphingolipid biosynthesis - globoseries	2	0.006197	St3gal2;B3galt5
Arachidonic acid metabolism	4	0.005752	Ptgds;Pla2g6;Ptgds2;Ptges
Benzoate degradation via CoA ligation	2	0.004998	Hadha;Echs1
Basal cell carcinoma	4	0.003407	Fzd5;Fzd9;Wnt5b;Gli2
Hedgehog signaling pathway	4	0.003407	Bmp8a;Csnk1d;Wnt5b;Gli2
Leukocyte transendothelial migration	6	0.002983	Plcg2;Cldn3;Thy1;Vav2;Rho;Cldn22
Caprolactam degradation	2	0.002963	Hadha;Echs1
Type II diabetes mellitus	4	0.002729	Cacna1e;Prkcz;Tnf;Abcc8
Hematopoietic cell lineage	5	0.002344	Il1a;Il6ra;Tnf;Il11;Cd7
Lysine degradation	4	0.001815	MGC109340;Ogdhl;Hadha;Echs1
Long-term depression	5	0.001528	Npr1;Grm5;Pla2g6;Nos2;Itpr2
Primary immunodeficiency	4	8.31E-04	Ikbkg;Zap70;Rfxank;Tap2
ABC transporters - General	4	7.43E-04	Abca1;Tap2;Abcc8;Abcb6
N-Glycan degradation	3	4.64E-04	Aga;RGD1310868;Neu4
TGF-beta signaling pathway	6	3.79E-04	Crebbp;Smad5;Tgfb1;Bmp8a;Tnf;Rps6kb2
Proteasome	5	3.48E-04	Psm7;Psm7;Psm11;Psm10;Psm8
Glycerophospholipid metabolism	5	3.16E-04	Ptdss1;Dgkz;Lcat;Pla2g6;Chkb
Biosynthesis of unsaturated fatty acids	4	2.59E-04	Elovl2;Hadha;Elovl5;Gpsn2
PPAR signaling pathway	6	2.27E-04	Angptl4;Slc27a6;Fabp6;Pparg;Cpt1b;Slc27a1

Tryptophan metabolism	5	2.11E-04	Aanat;Ogdhl;Hadha;Echs1;Mettl6
Complement and coagulation cascades	6	1.79E-04	F5;C8g;Masp1;F10;Serpinf2;C4b
Tight junction	8	1.68E-04	Llgl1;Pard6b;Myh7b;Cldn3;Prkcz;Src;Rras;Cldn22
Gap junction	7	1.24E-04	Csnk1d;Npr1;Tubb3;Grm5;Src;Itpr2;Tuba3a
Androgen and estrogen metabolism	5	9.28E-05	Hsd17b1;Sult2b1;Ugt1a2;Ugt1a1;Mettl6
Cytokine-cytokine receptor interaction	13	8.35E-06	Il1a;LOC500598;Il6ra;Cx3cr1;Tgfb1;Tnfsf13;Tnfrsf1a;Bmp8a;Cd27;Tnf;Lta;Il11;Ccl11
MAPK signaling pathway	16	1.48E-07	Il1a;Cacna1e;Ikbkg;Fgfr3;Tgfb1;Tnfrsf1a;Dusp1;Tnf;Pla2g6;Map4k3;Rras;Flnb;Cacna1i;Cacnb2;Map3k4;Srf
Calcium signaling pathway	19	2.58E-12	Cacna1e;Plcg2;Tbxa2r;Ptger1;Adrb2;P2rx7;Ntsr1;Ryr2;Adra1d;Htr5a;Tnnc2;Drd5;Grm5;Nos2;Adora2a;Itpr2;Chrm1;Gna15;Cacna1i
Neuroactive ligand-receptor interaction	26	7.87E-15	Grin2b;Tbxa2r;Prlh;Ptger1;Adrb2;P2rx7;Pth2r;Mc3r;Ntsr1;Tspo;Galr2;Oxt;Oprl1;Adra1d;Hrh4;Htr5a;Drd5;Aplnr;Grm5;Avp;Adora2a;Crhr2;Chrm1;Grp;Mas1;Ucn2

Supplementary Table 2. Pathways of changes in hypomethylation in F1 offspring exposed to intrauterine hyperglycemia

Pathway	Enrichment Score (-log ₁₀ [P value])	p-value	gene
Adipocytokine signaling pathway	8	3.70E-04	Camkk2;Pck1;Rxb;Adipoq;Tnf;Prkag3;Nfkbib;Mapk10
Glycerophospholipid metabolism	7	3.39E-04	Dgkb;Pemt;Cdipt;Agpat1;Lcat;Phospho1;Ppap2c
Glycosphingolipid biosynthesis - lactoseries	5	3.28E-04	B3gnt4;St3gal6;Fut7;Fut1;B4galt2
Type II diabetes mellitus	7	2.98E-04	Prkce;Prkcz;Adipoq;Tnf;Slc2a2;Prkcd;Mapk10
Insulin signaling pathway	12	2.86E-04	Pck1;Gys2;Ppp1r3b;Bad;Shc2;Inpp5d;Prkcz;Rps6kb2;Shc1;Prkar2a;Prkag3;Mapk10
TGF-beta signaling pathway	9	2.65E-04	Rbl2;Tgfb2;Ltbp1;Rps6kb2;Tnf;Tgfb1;Smad1;Id4;Bmp8a
GnRH signaling pathway	10	1.84E-04	Mmp14;Adcy4;Mmp2;Gnas;Map2k6;Mapk12;Prkcb;Prkcd;Itpr3;Mapk10
Citrate cycle (TCA cycle)	6	1.34E-04	Idh3a;Pck1;Idh2;Pdha1;Idh3g;Sdhb
VEGF signaling pathway	9	1.28E-04	Bad;Ppp3r2;Shc2;Mapk12;Mapkapk2;Nfatc4;Prkcb;Rac2;Ptk2
Leukocyte transendothelial migration	12	7.81E-05	Icam1;Mmp2;Mapk12;Ocln;Prkcb;Itgb2;Cldn9;Actn1;Rap1a;Rac2;Ptk2;Pecam1
Taste transduction	7	7.69E-05	Adcy4;Tas2r134;Gnas;Scnn1a;Itpr3;Tas2r126;Kcnb1
Hedgehog signaling pathway	8	6.52E-05	Csnk1g3;Csnk1g2;Sufu;Gli2;Wnt8a;Bmp8a;Wnt7b;Btrc
Natural killer cell mediated cytotoxicity	14	3.49E-05	Icam1;Slc39a7;Cd244;Ppp3r2;Shc2;Nfatc4;Prkcb;Itgb2;Shc1;Tnf;Tnfrsf10b;Rac2;Ifngr2;Ifna4
Purine metabolism	14	2.75E-05	Hprt1;Paics;Polr2h;Polr2hl;Nme3;Nt5e;Adcy4;Pde9a;Polr2i;Polr2c;Pde2a;Polr1c;Pde8b;Xdh
Cell adhesion molecules (CAMs)	15	1.57E-05	Cdh15;Icam1;Mag;Ctla4;Pvrl3;Slc39a7;Madcam1;LOC288521;Cntn1;L1cam;Ocln;Itgb2;Cldn9;Cd8a;Pecam1
Toll-like receptor signaling pathway	12	8.35E-06	Map3k7;Tlr5;Cxcl9;Tlr2;Cd14;Map2k6;Mapk12;Tnf;Irak4;Myd88;Mapk10;Ifna4
Hematopoietic cell lineage	11	6.43E-06	Tpo;Epo;Fcer2;Cd14;Anpep;Gp1bb;Csf3;Tnf;Cd8a;Cd37;Kit
PPAR signaling pathway	11	3.25E-06	Pck1;Rxb;Acox2;Olr1;Cyp7a1;Ucp1;Adipoq;Acaa1;RGD1562373;Fads2;Aqp7

Wnt signaling pathway	16	1.44E-06	Map3k7;Ctbp1;Tbl1xr1;Apc2;Ppp3r2;Nfatc4;Prkcb;Wnt8a;Axin2;Ppp2r5b;Rac2;Prickle1;Wnt7b;Csnk2b;Mapk10;Btrc
Focal adhesion	19	1.03E-06	Flt4;Bcl2;Pdgfa;Egf;Bad;Mylk2;Shc2;Itga7;Itga11;Prkcb;Shc1;lbsp;Actn1;Rap1a;Rac2;Itga10;Ptk2;Mapk10;Lamc3
Jak-STAT signaling pathway	17	2.85E-07	Tpo;Epo;Prlr;Il21;Csf3;Spred2;Osm;Il9;Cntfr;Clcf1;Stat5a;Prl;Il24;Ifngr2;Irf9;Il10rb;Ifna4
Tight junction	17	6.77E-08	Prkce;Prkch;Myh7b;LOC304000;Rab3b;Myh6;Tjp2;Myh3;Prkcz;Ocln;Prkcb;Rab13;Cttn;Cldn9;Actn1;Prkcd;Csnk2b
Regulation of actin cytoskeleton	24	2.27E-09	Was;Bdkrb2;Pdgfa;Apc2;F2r;Egf;Chrm2;Cd14;Mylk2;Bdkrb1;Itga7;Itga11;Itgad;Fgf21;Arhgef6;Itgb2;Gsn;Ssh3;Actn1;Wasf2;Rac2;Fgf16;Itga10;Ptk2
Axon guidance	19	1.53E-09	Dpysl2;Efna5;Efnb3;Sema6c;Sema3f;Efna4;Ppp3r2;L1cam;Epha2;Nfatc4;Plxnb3;Ephb3;Cdk5;Epha3;Robo1;Epha1;Rac2;Sema4f;Ptk2
Complement and coagulation cascades	17	2.56E-12	C4b;Bdkrb2;F10;Serping1;F2r;Bdkrb1;Serpinc1;F3;Fgb;Cfi;F8;Kng1;C1qa;C1qb;C4bpa;Serpina5;C2
MAPK signaling pathway	32	1.29E-12	Map3k7;Tgfb2;Mapk6;Ecsit;Pdgfa;Cacng5;Cacna1i;Egf;Cd14;Map2k6;Rasa2;Ppp3r2;Mapk12;Mapkapk2;Rps6ka1;Cacnb4;Nfatc4;Stk3;Prkcb;Fgf21;Cacng8;Rasgrp3;Ptpn5;Tnf;Tgfb1;Rap1a;Cacng1;Rac2;Ptpn7;Fgf16;Ntf4;Mapk10
Calcium signaling pathway	29	5.83E-14	Adra1a;Grpr;Bdkrb2;Atp2b3;Tnnc1;Adcy4;Cacna1i;Vdac3;F2r;Gnas;Chrm2;Ptgfr;Avpr1b;Mylk2;Ppp3r2;Ptger1;Bdkrb1;Nos1;Slc8a2;Prkcb;Plce1;Lhcgr;Adrb1;Drd1a;Htr6;Ltb4r2;P2rx1;Trhr2;Itpr3
Cytokine-cytokine receptor interaction	37	1.23E-17	Tpo;Flt4;Epo;Cx3cl1;Relt;Tgfb2;Cxcl9;Prlr;Ccl26;Il8rb;Pdgfa;Il18r1;Egf;Ccl17;Tnfrsf25;Il21;Csf3;Osm;Il9;Ltbr;Cntfr;Clcf1;Tnf;Lta;Tgfb1;Ccl4;LOC301289;Bmp8a;Kit;Tnfrsf21;Prl;Tnfrsf10b;Il24;Ifngr2;Il10rb;Ccr6;Ifna4
Olfactory transduction	72	1.41E-20	Olr1401;Olr1768;Olr139;Olr1454;Olr62;Olr140;Olr107;Olr1592;Olr495;Olr288;Olr859;Olr1335;Olr144;Olr837;Olr462;Olr1092;Olr45;Olr78;Olr1456;Olr1702;Olr1765;Olr1644;Olr156;Olr1612;Olr1387;

			<p>Olr840;Olr856;Olr1645; Olr84;Olr1l;Olr303;Olr857;Olr1432;Olr425;Olr1686;Olr321;Olr875;Olr43;Olr69;Olr448; Olr1091;Olr4;Olr836;Olr1744;Olr153;Olr154;Olr1090;Olr1344;Olr434;Olr1568;Olr1413; Olr838;Olr113;Olr300;Olr307;Olr1309;Olr142;Olr1657;Olr1337; Olr149;Olr483;Olr130;Olr1595;Olr1334;Olr1096;Olr1106;Olr1198;Olr1306;Olr148; Olr1111;Olr168;Olr1093</p>
Neuroactive ligand-receptor interaction	50	8.78E-25	<p>Gpr83;Adra1a;Glp1r;Grpr;Galr1;Ppyr1;P2ry14;Prlr;Fshr;Bdkrb2;Ptgir;Nmur1;Grp; F2r;Ltb4r;Chrm2;Ptgfr;Tac4; Avpr1b;Grm2;Ptger1;Bdkrb1;Hcrt;Gpr156;Mtnr1a;Gpr35;Gabrg2;Lhcgr;Adrb1; Ppy;Grik5;S1pr4;Uts2;Ucn2;Drd3; Taar1;Drd1a;Glp2r;Ucn2;P2ry13;Kiss1r;Htr6;Ltb4r2;Hcrr1;Sstr3;Prl;P2rx1; Trhr2;Tac2;P2ry4;Cnr2</p>

Supplementary Figure 1

