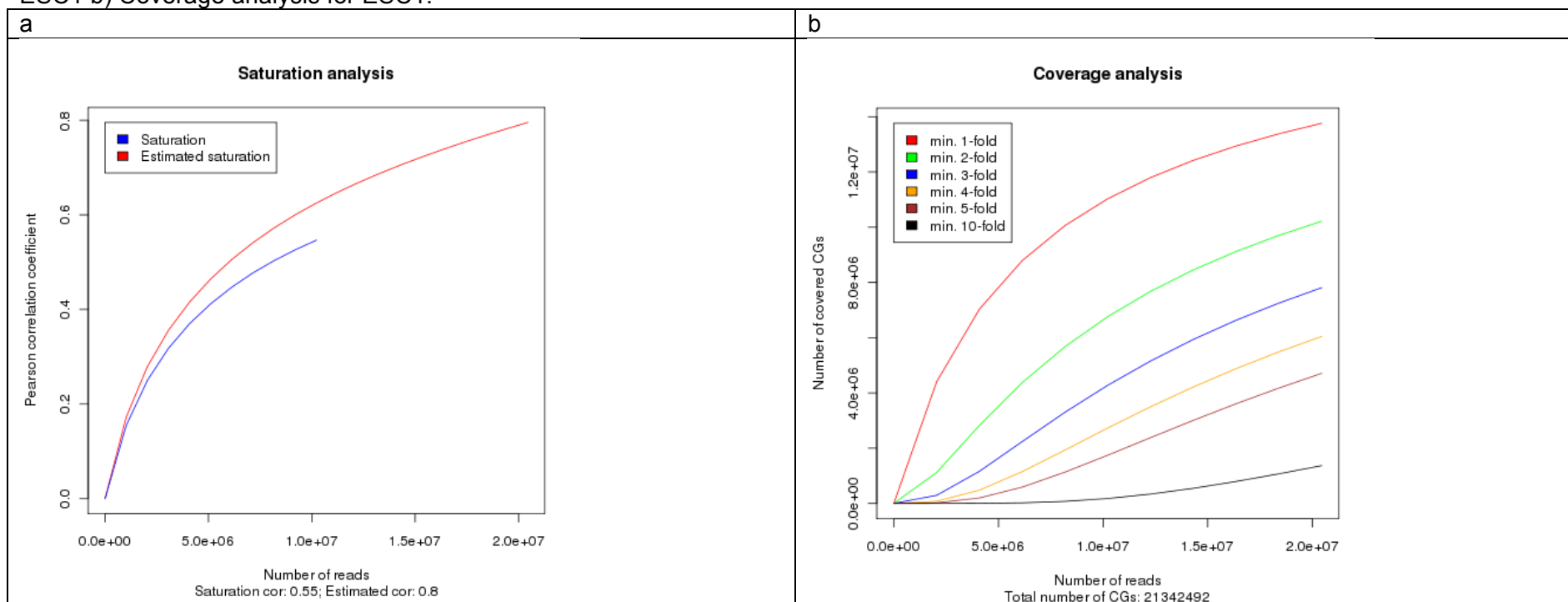


Supplementary Material

Supplementary Figure 1

Example of saturation and coverage analysis, performed in MeDUSA using the MEDIPS bioconductor package. a) Saturation analysis for ESC1 b) Coverage analysis for ESC1.



Supplementary Figure 2

Methylomes available through Ensembl (Flicek et al. 2011) as part of the EU project HEROIC.

CAG
TAT
ATC
CAG
TAT
CAA
GTA
ATG
TGA
TCC
GGTA
GATG

 **Ensembl Projects**
The HEROIC Project
High-throughput Epigenetic Regulatory Organisation In Chromatin

epigenetic research.

Beck

18 methylomes of Mouse ES & NP TDG heterozygotes and knockouts

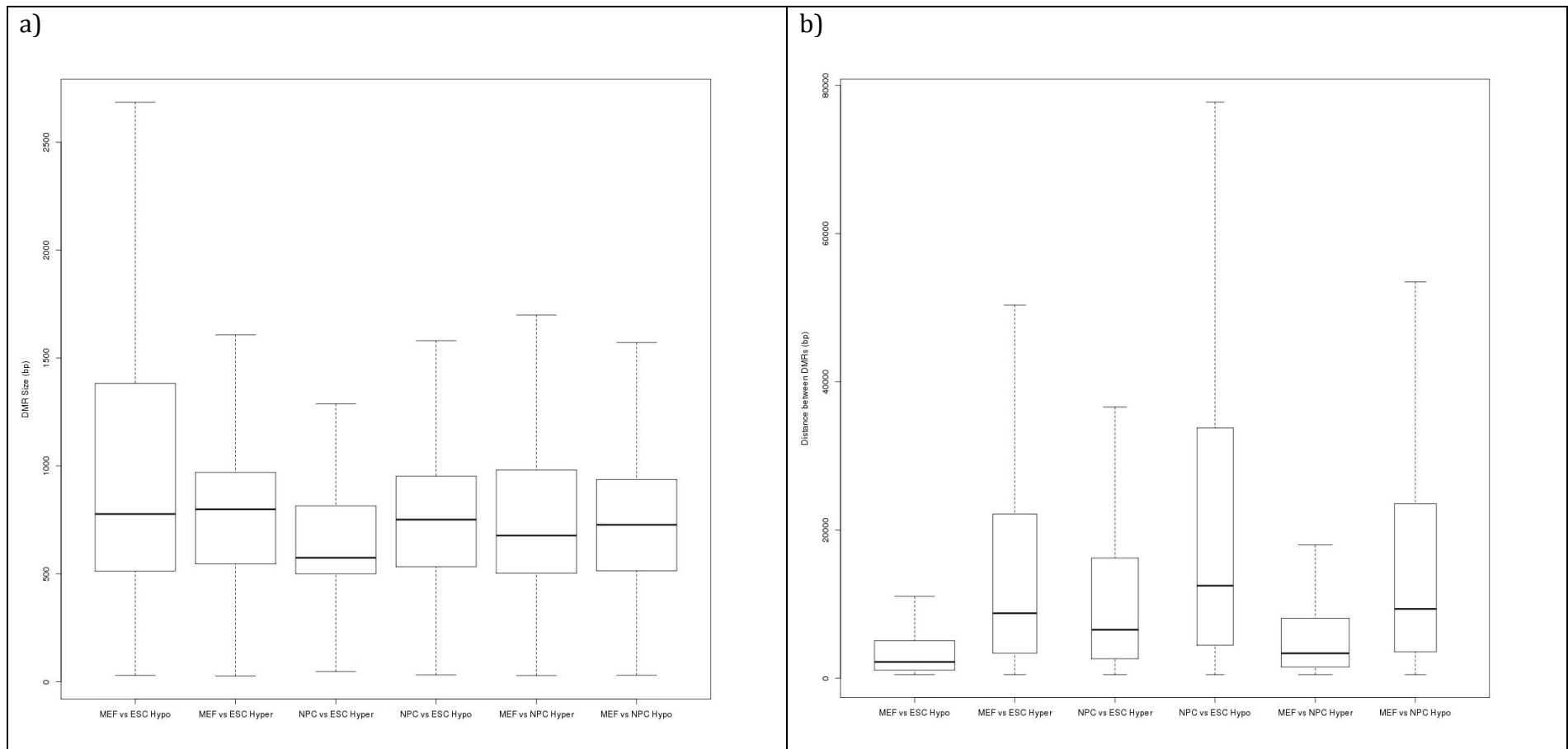
Medip-Seq

Manuscript GSE27468 in preparation

TCT
AAAA
GTGT
AGCA
GAAA
GGAT
CAAG
AAAG
TGAA
TCTA
CAAG
AAAG

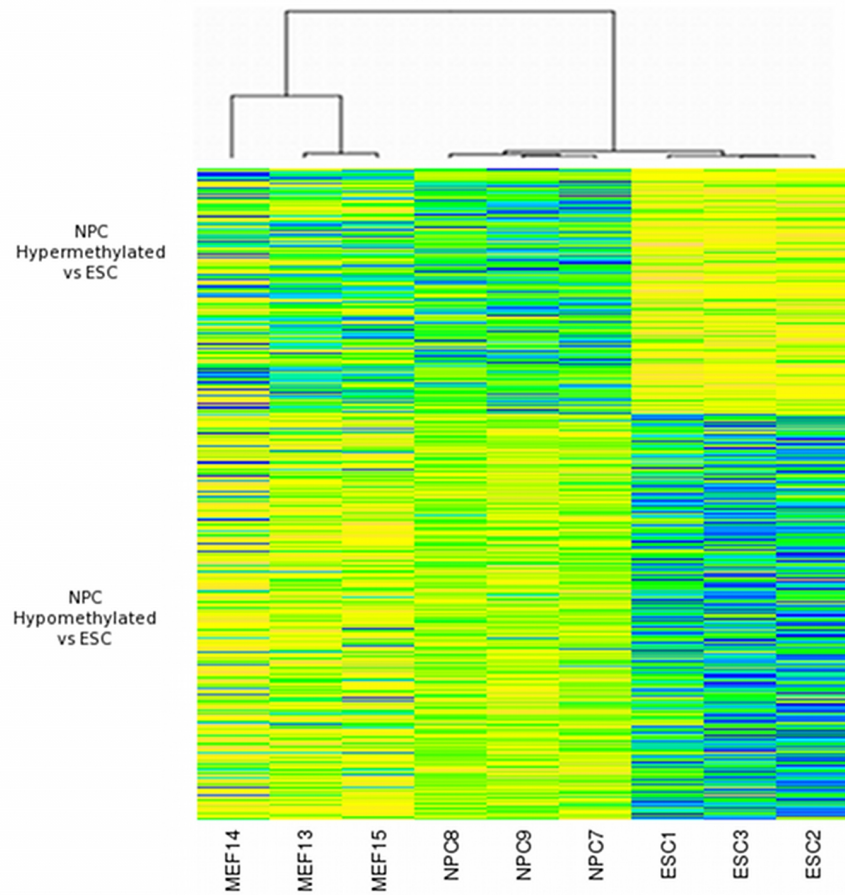
Supplementary Figure 3

Boxplots displaying a) the DMR size (bp) and b) the genomic distance between DMRs across different cohort comparisons. In b) the width of each box represents the relative number of DMRs in the comparison.



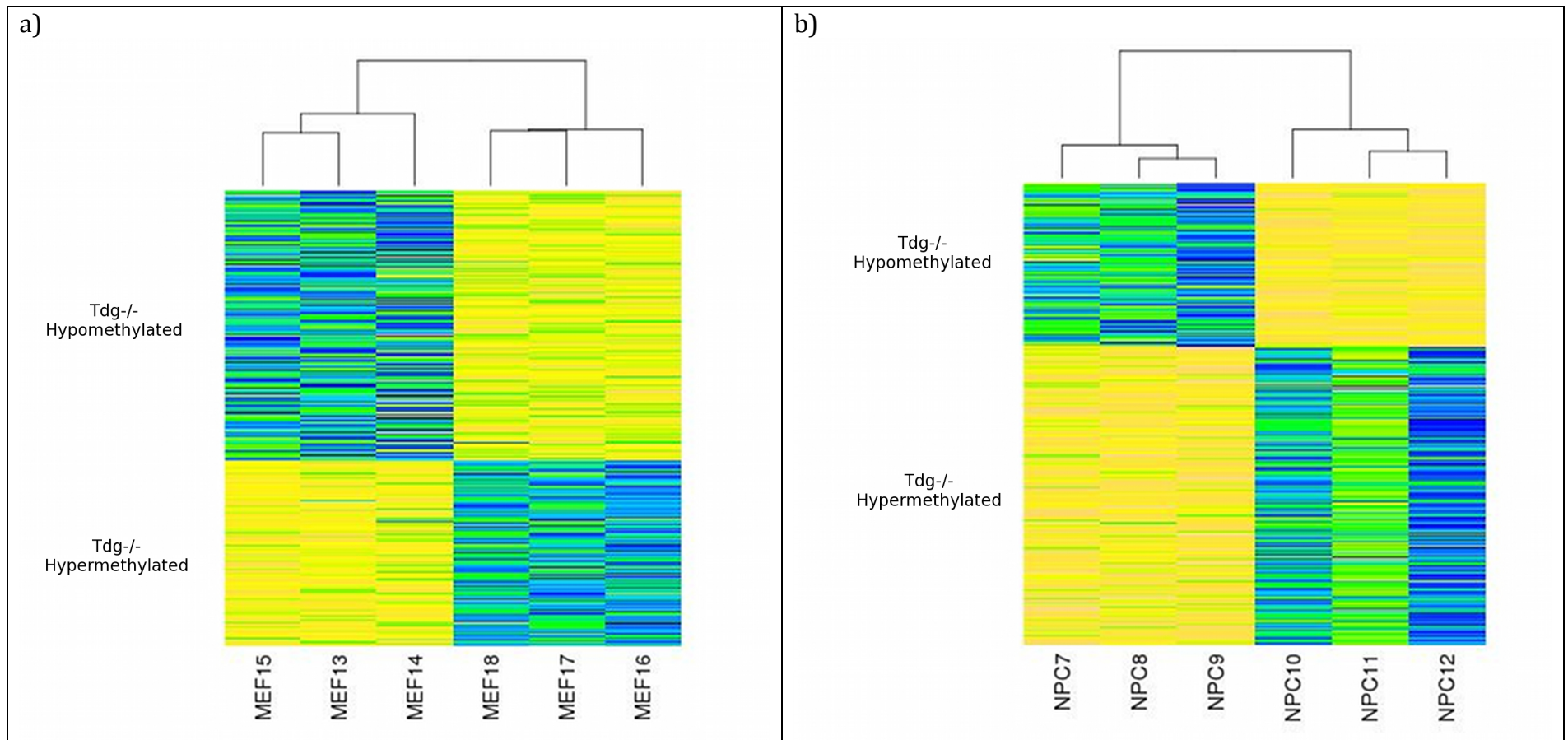
Supplementary Figure 4

Read density (RPM) at DMRs found between NPC and ESC cohorts. MEF RPM also shown for these sites.



Supplementary Figure 5

Read density (RPM) at DMRs between a) MEF *Tdg*^{+/+} and MEF *Tdg*^{-/-} b) NPC *Tdg*^{+/+} and NPC *Tdg*^{-/-}

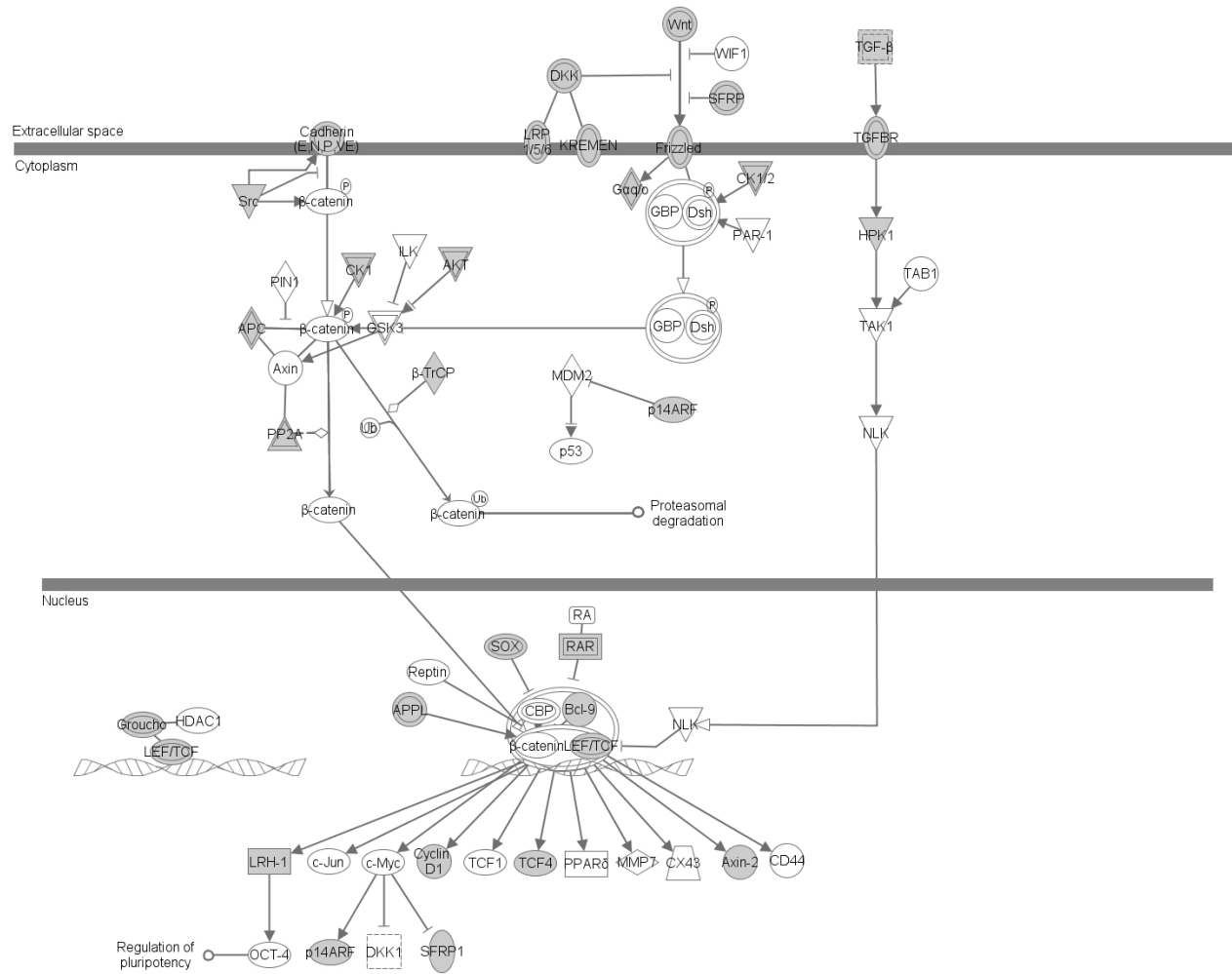


Supplementary Figure 6

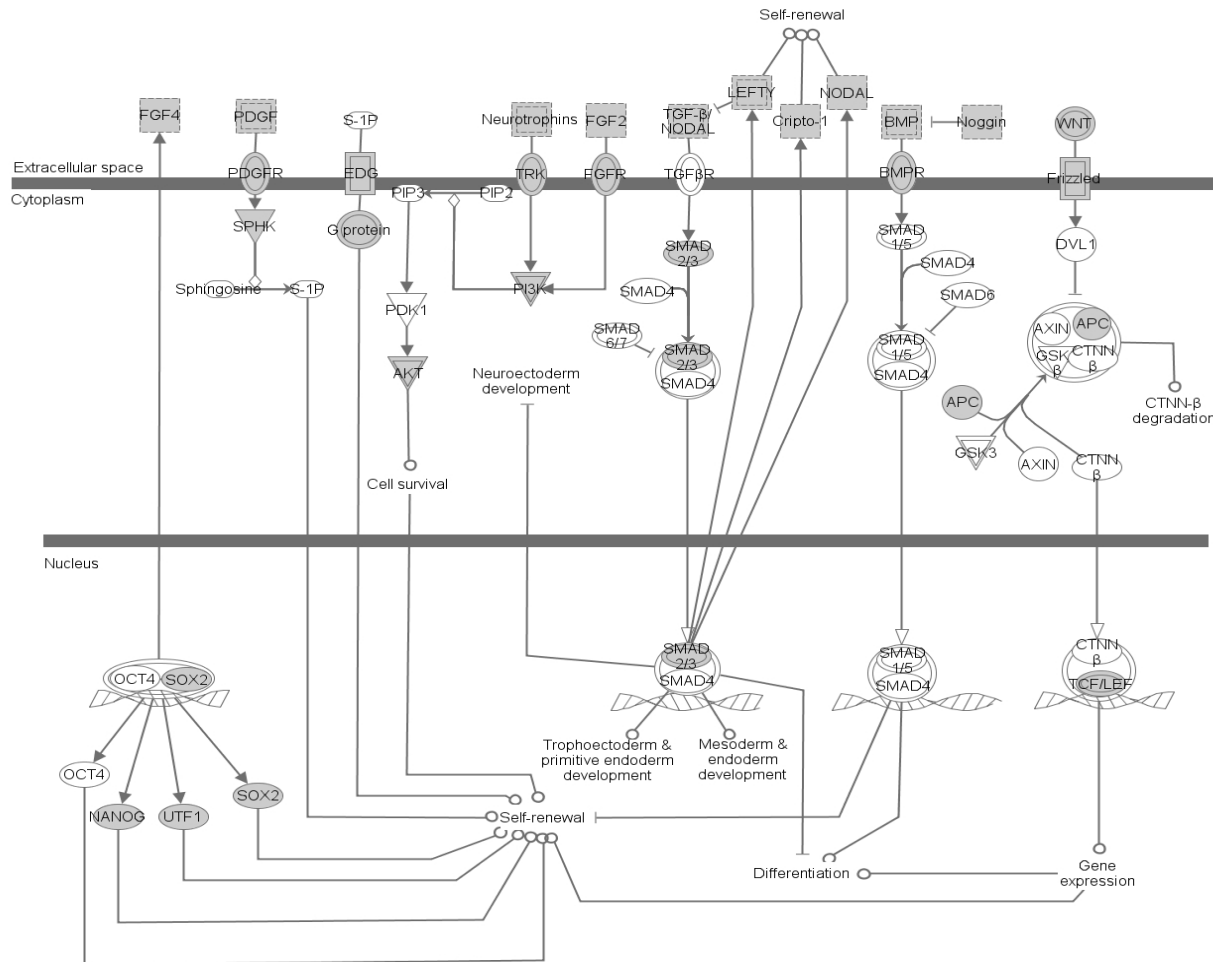
Significant pathways obtained from IPA Canonical Pathway Analysis (Ingenuity® Systems, www.ingenuity.com). Filled symbols represent genes associated with DMRs. a) Enrichment of hypermethylated MEF *Tdg*^{-/-} DMRs associated with Wnt signaling pathway. 95 of 172 genes associated with DMR (BH corrected p-value = 4.15E-11), b) Enrichment of hypermethylated MEF *Tdg*^{-/-} DMRs associated with embryonic stem cell pluripotency pathway (human). 78 of 153 genes associated with DMR (BH corrected p-value = 8.57E-11).

a

Wnt/ β -catenin Signaling



b
Human Embryonic Stem Cell Pluripotency



Supplementary Table 1

18 mouse methylomes, representing 6 biological cohorts, were generated using PE MeDIP-seq

Sample	Genotype	Cycles	Total Reads (pre-alignment)	Unique fragments (paired reads)	Mean Insert Size	CpG Enrichment Score	CpG coverage	%GC
ESC1	<i>Tdg</i> ^{+/-}	36	62845000	20341082	151.78	2.29	65.20%	45
ESC2	<i>Tdg</i> ^{+/-}	36	62364152	10709640	149.15	2.51	49.13%	48
ESC3	<i>Tdg</i> ^{+/-}	36	54406944	14817391	141.17	2.57	54.99%	48
ESC4	<i>Tdg</i> ^{-/-}	36	66927428	17614895	173.89	2.54	59.02%	49
ESC5	<i>Tdg</i> ^{-/-}	36	65322058	14589787	167.09	2.48	55.27%	48
ESC6	<i>Tdg</i> ^{-/-}	36	44856148	15827404	143.37	2.49	58.42%	47
NPC7	<i>Tdg</i> ^{+/-}	36	45656784	15525293	158.85	3.11	54.44%	48
NPC8	<i>Tdg</i> ^{+/-}	36	50774190	17196263	153.37	3.03	56.40%	48
NPC9	<i>Tdg</i> ^{+/-}	36	67152858	16996748	147.37	3.16	53.65%	48
NPC10	<i>Tdg</i> ^{-/-}	36	66567040	17297064	153.99	3.00	54.88%	47
NPC11	<i>Tdg</i> ^{-/-}	36	69551064	21441777	152.98	3.10	58.85%	48
NPC12	<i>Tdg</i> ^{-/-}	36	72155140	23156257	165.49	3.00	60.72%	48
MEF13	<i>Tdg</i> ^{+/+}	36	47189760	9409098	149.91	3.91	34.12%	44
MEF14	<i>Tdg</i> ^{+/+}	36	16940284	3160066	131.32	4.6	17.39%	45
MEF15	<i>Tdg</i> ^{+/+}	36	32206682	6621484	163.02	3.81	30.55%	44
MEF16	<i>Tdg</i> ^{-/-}	36	40284500	8645926	147.21	4.59	32.47%	45
MEF17	<i>Tdg</i> ^{-/-}	36	45055076	9349976	153.37	4.47	34.00%	44
MEF18	<i>Tdg</i> ^{-/-}	36	42421696	8794422	147.32	4.51	32.63%	45

Supplementary Table 2

Between replicate MeDIP-seq correlations, generated by QCSeqs, for the methylomes

	ESC1	ESC2	ESC3	ESC4	ESC5	ESC6	NPC7	NPC8	NPC9	NPC10	NPC11	NPC12	MEF13	MEF14	MEF15	MEF16	MEF17	MEF18
ESC1		0.53	0.51	0.55	0.52	0.54												
ESC2	0.53		0.63	0.57	0.56	0.63												
ESC3	0.51	0.63		0.55	0.54	0.66												
ESC4	0.55	0.57	0.55		0.61	0.56												
ESC5	0.52	0.56	0.54	0.61		0.54												
ESC6	0.54	0.63	0.66	0.56	0.54													
NPC7								0.83	0.84	0.83	0.87	0.85						
NPC8							0.83		0.85	0.83	0.86	0.82						
NPC9							0.84	0.85		0.84	0.88	0.83						
NPC10							0.83	0.83	0.84		0.87	0.87						
NPC11							0.87	0.86	0.88	0.87		0.87						
NPC12							0.85	0.82	0.83	0.87	0.87							
MEF13														0.90	0.92	0.76	0.77	0.77
MEF14													0.90		0.91	0.75	0.76	0.77
MEF15													0.92	0.91		0.73	0.75	0.75
MEF16													0.76	0.75	0.73		0.94	0.94
MEF17													0.77	0.76	0.75	0.94		0.94
MEF18													0.77	0.77	0.75	0.94	0.94	

Supplementary Table 3

Summarised output from GREAT analysis (McLean et al. 2010). a) Hypermethylated in MEF *Tdg*^{-/-}, b) Hypomethylated in MEF *Tdg*^{-/-}.

a)

Ontology	Term Name	Binom FDR Q-Val	Hyper FDR Q-Val
GO Molecular Function	transcription regulator activity	0	2.57E-37
GO Molecular Function	DNA binding	0	2.12E-21
GO Molecular Function	nucleic acid binding	0	5.22408E-05
GO Molecular Function	transcription factor activity	1.2257e-319	6.43E-39
GO Molecular Function	sequence-specific DNA binding	1.765e-319	1.59E-36
GO Biological Process	system development	0	4.82E-66
GO Biological Process	multicellular organismal development	0	2.58E-66
GO Biological Process	anatomical structure development	0	1.20E-62
GO Biological Process	developmental process	0	9.61E-63
GO Biological Process	organ development	0	3.50E-48
GO Biological Process	regulation of metabolic process	0	4.90E-29
GO Biological Process	regulation of cellular metabolic process	0	6.33E-29
GO Biological Process	regulation of primary metabolic process	0	2.98E-26
GO Biological Process	regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolic process	0	4.70E-23
Mouse Phenotype	nervous system phenotype	0	7.21E-80
Mouse Phenotype	abnormal nervous system morphology	6.50E-299	1.46E-55
Mouse Phenotype	lethality-prenatal/perinatal	1.34E-271	2.84E-34
PANTHER Pathway	Wnt signaling pathway	1.52E-33	8.37E-07
MSigDB Pathway	Pathways in cancer	3.01E-45	1.38E-12
MSigDB Pathway	MAPK signaling pathway	4.81E-30	1.21445E-06

MSigDB Pathway	Basal cell carcinoma	8.21E-29	9.02E-08
MSigDB Pathway	Wnt signaling pathway	1.79E-25	1.26463E-06
MSigDB Pathway	Genes related to Wnt-mediated signal transduction	1.90E-24	2.44941E-05
MGI Expression: Detected	TS20_organ system	0	3.18E-66
MGI Expression: Detected	TS20_embryo	0	3.26E-65
MGI Expression: Detected	Theiler_stage_20	0	8.15E-62
MGI Expression: Detected	TS17_embryo	0	9.61E-55
MSigDB Perturbation	Set 'H3K27 bound': genes possessing the trimethylated H3K27 (H3K27me3) mark in their promoters in human embryonic stem cells, as identified by ChIP on chip.	0	1.75E-158
MSigDB Perturbation	Set 'Eed targets': genes identified by ChIP on chip as targets of the Polycomb protein EED [Gene ID=8726] in human embryonic stem cells.	0	9.87E-121
MSigDB Perturbation	Set 'Suz12 targets': genes identified by ChIP on chip as targets of the Polycomb protein SUZ12 [Gene ID=23512] in human embryonic stem cells.	0.00E+00	3.20E-136
MSigDB Perturbation	Set 'PRC2 targets': Polycomb Repression Complex 2 (PRC) targets; identified by ChIP on chip on human embryonic stem cells as genes that: possess the trimethylated H3K27 mark in their promoters and are bound by SUZ12 [Gene ID=23512] and EED [Gene ID=8726] Polycomb proteins.	1.11E-281	3.17E-107

b)

Ontology	Term Name	Binom FDR Q-Val	Hyper FDR Q-Val
GO Molecular Function	cation channel activity	1.97E-46	8.42E-13
GO Molecular Function	voltage-gated ion channel activity	1.36E-45	2.80E-08
GO Molecular Function	voltage-gated cation channel activity	5.04E-36	2.13825E-06
GO Molecular Function	potassium channel activity	1.79E-27	1.61838E-06
GO Biological Process	extracellular structure organization	1.22E-38	0.000483757
GO Biological Process	potassium ion transport	1.07E-28	3.05244E-06
GO Biological Process	divalent metal ion transport	1.98E-28	0.000494935
MGI Expression: Detected	TS17_surface ectoderm	6.96E-53	2.06E-11

MGI Expression: Detected	TS17_embryo;ectoderm	3.38E-50	2.06E-11
MGI Expression: Detected	TS17_urogenital system	3.86E-40	9.21E-10