

Fig. S1. The concept of evolutionary transgenerational systems biology.

A representation of the conceptual mechanistic framework proposed previously (Sharma, 2014; Sharma, 2015a-c) to explain transgenerational epigenetic inheritance and its evolutionary significance. The model, supported by qualitative evidence, suggests that epigenetic inheritance of acquired traits may result in mutational fixation of the epiallele in evolutionary time course.

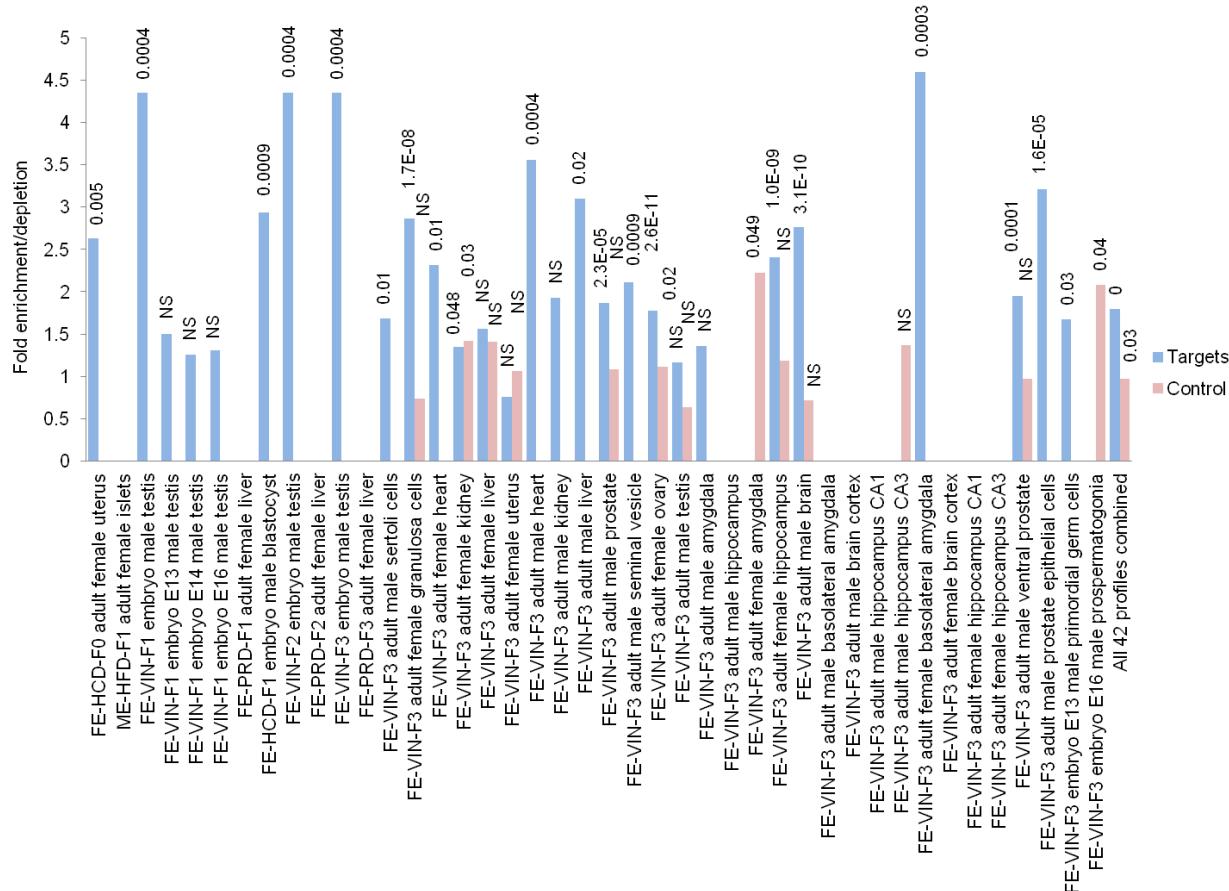


Fig. S2. Enrichment of validated target genes of common miRNAs, total 708 in number (Table S8), in differentially expressed mRNAs reported in studies on epigenetic inheritance in rat. Note combined analysis, represented by the extreme right pair of bars, showing enrichment of the targets in mRNAs reported in epigenetic studies. Key to mRNA expression profiles: gender exposed at F0-treatment at F0-generation, stage, gender and sample profiled. ME, male exposure; FE, female exposure; HFD, high fat diet; VIN, vinclozolin; PRD, protein restricted diet; HCD, high calorie diet. Enrichment *P* values, hypergeometric distribution, are shown above bars. NS, not significant. Missing bars indicate overlapping counts as either nil or excessively low, considered inappropriate for analysis.

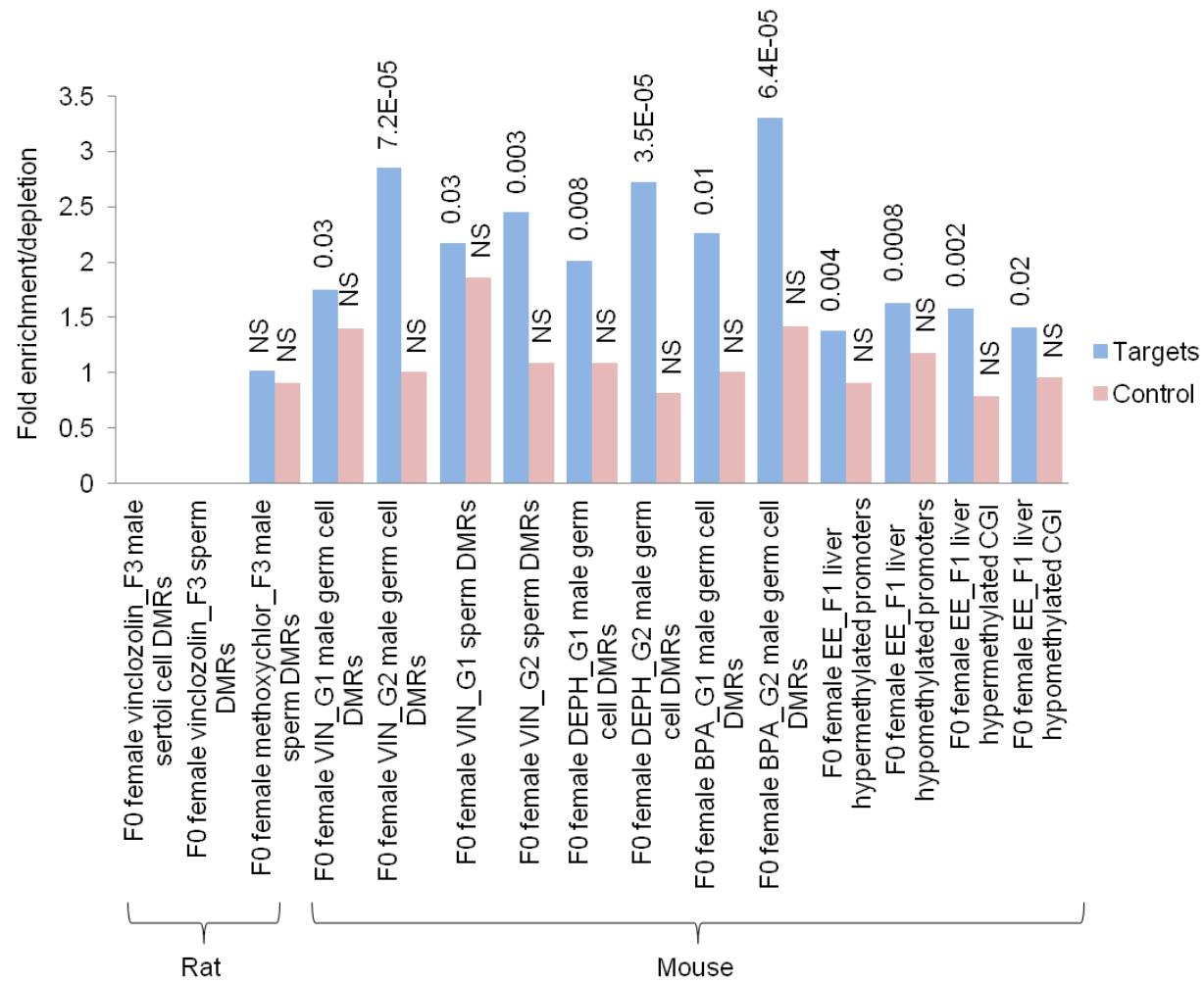


Fig. S3. Overrepresentation of targets (Fig. S2) in differentially methylated genes reported in studies on epigenetic inheritance. Key to DNA methylation profiles: gender and environmental factor used for exposure at F0-generation, gender, sample and DNA elements profiled. DEPH, di-(2-ethylhexyl)phthalate; EE, environmental enrichment; DMRs, differentially methylated regions; CGI, CpG island. Enrichment *P* values, hypergeometric distribution, are shown above bars. NS, not significant. Missing bars indicate overlapping counts as either nil or excessively low, considered inappropriate for analysis.

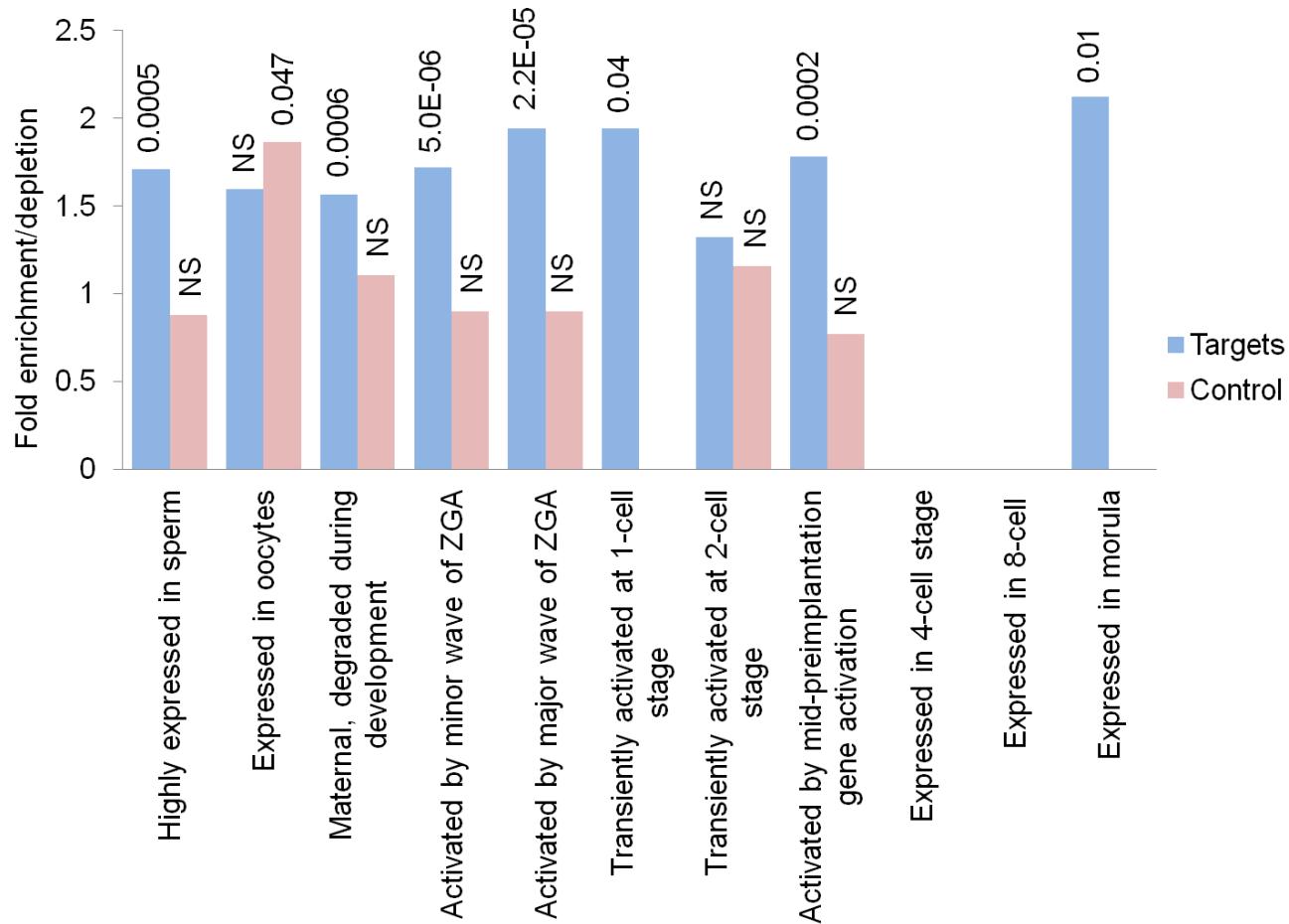


Fig. S4. Gene expression in gametes, zygote and postzygotic stages. Overall, the targets tend to enrich genes expressed in sperm, oocytes, zygote and developing embryo. ZGA, zygotic gene activation. Enrichment *P* values, hypergeometric distribution, are shown above bars. NS, not significant. Missing bars indicate overlapping counts as either nil or excessively low, considered inappropriate for analysis.

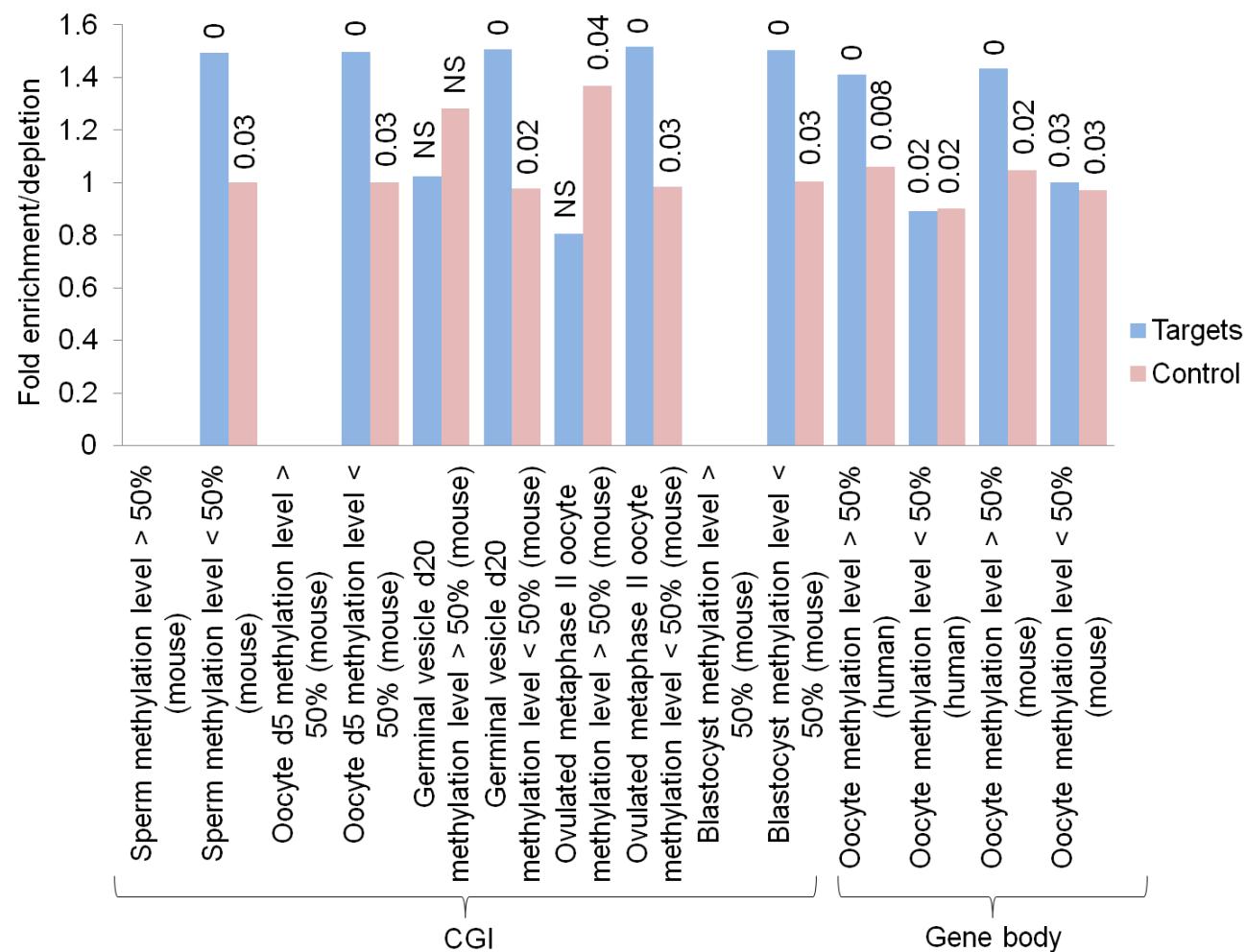


Fig. S5. DNA methylation levels in gametes and developing embryo. The targets in general overrepresent genes with < 50%, and underepresent genes with > 50% CpG island (CGI) methylation levels. For gene body levels, the targets enrich genes with > 50% methylation, without showing any trend for over- or under-representation of genes with < 50% levels. Enrichment *P* values, hypergeometric distribution, are shown above bars. Values with 16 or more negative exponent of 10 were rounded down to zero. NS, not significant. Missing bars indicate overlapping counts as either nil or excessively low, considered inappropriate for analysis.

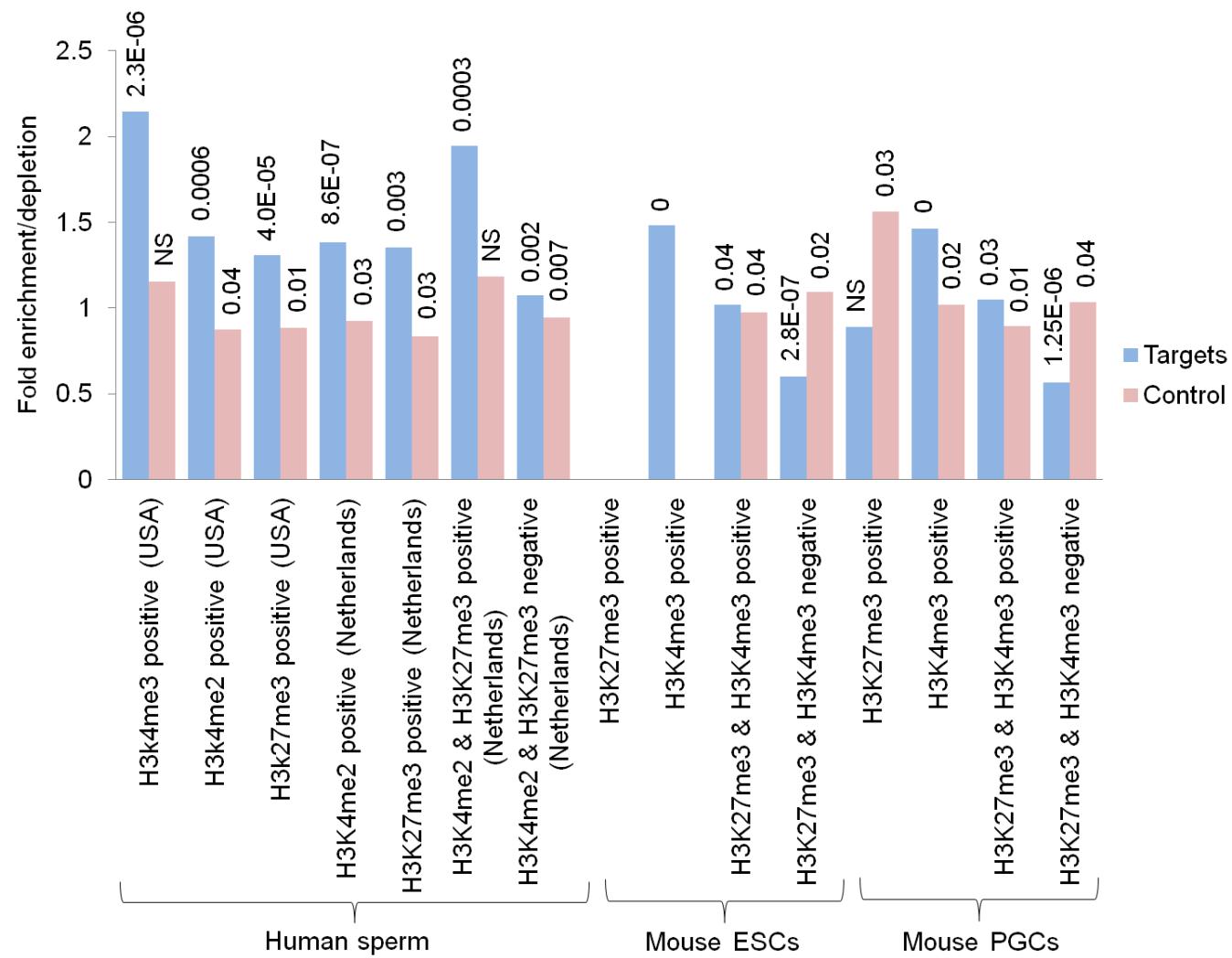


Fig. S6. Histone modifications in gametes and development. Note clear enrichment of the targets in H3K4me2, H3K4me3, and H3K27me3 positive genes in human sperm. The targets also show differential histone modifications in embryonic stem cells (ESCs) and PGCs. Enrichment *P* values, hypergeometric distribution, are shown above bars. Values with 16 or more negative exponent of 10 were rounded down to zero. NS, not significant. Missing bars indicate overlapping counts as either nil or excessively low, considered inappropriate for analysis.

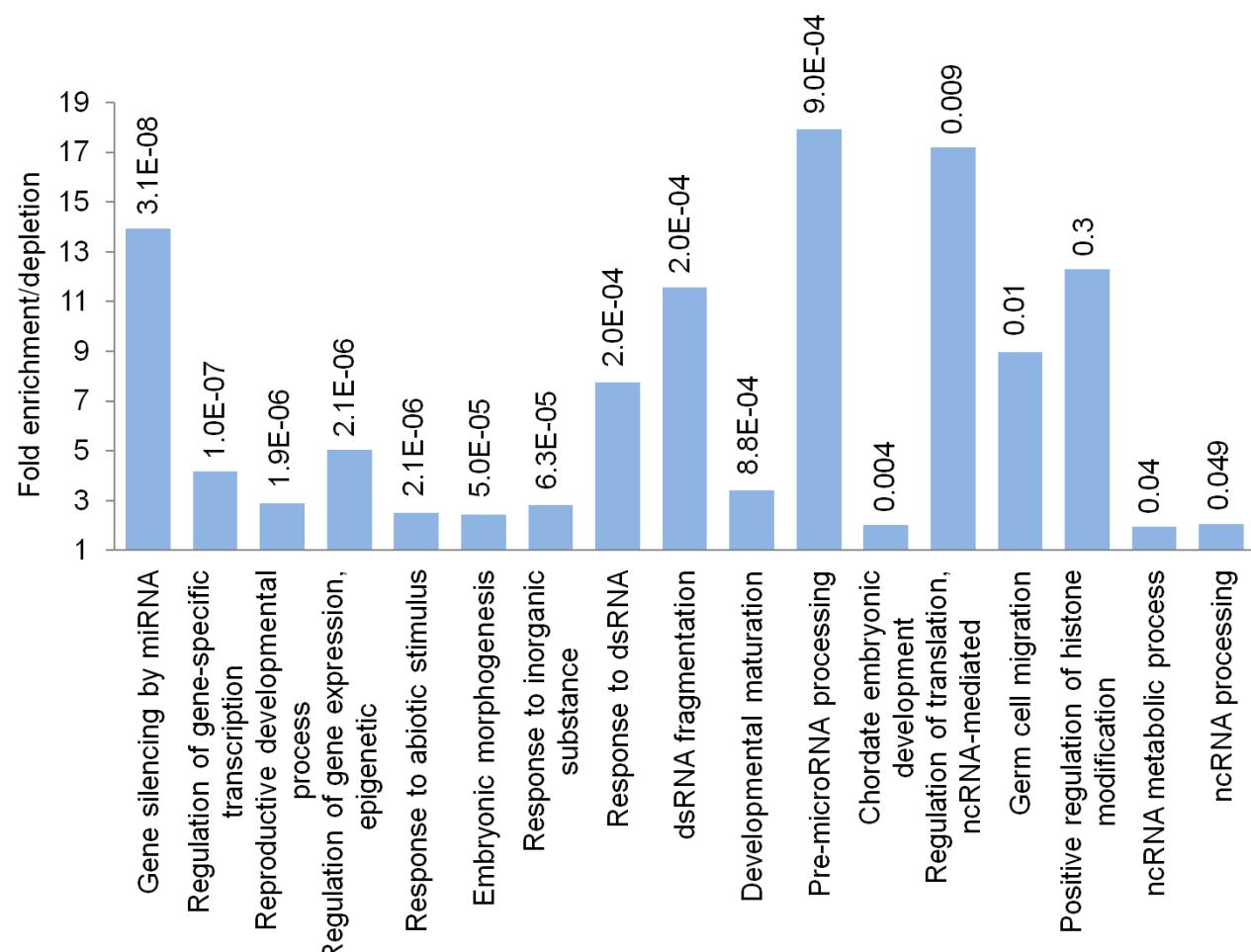


Fig. S7. Gene ontology biological process enrichment. A subset of processes enriched in the targets is shown. Control genes did not show enrichment/depletion of any process, as expected. Enrichment *P* values, hypergeometric distribution, are shown above bars.

Table S1

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Table S2

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Table S3

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Table S4

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Table S5. Data source used in the analysis shown in Fig. 2 and Figs. S2-S7

Figure label	Data source
ME-HFD-F0 testis	PubMed ID: 23845863
ME-LPD-F1 liver	PubMed ID: 21183072
ME-B[a]P-F1 embryo 2 cell	PubMed ID: 22548065
ME-B[a]P-F1 embryo 8 cell	PubMed ID: 22548065
ME-B[a]P-F1 embryo blastocyst	PubMed ID: 22548065
FE-stress-F1 sperm	PubMed ID: 24728267
ME-stress-F1 brain	PubMed ID: 23699511
ME-stress-F0 sperm	PubMed ID: 23699511
FE-BA-F1 fetal d 65 ovary	PubMed ID: 23525218
FE-BA-F1 fetal d 90 ovary	PubMed ID: 23525218
FE-T-F1 fetal d 90 ovary	PubMed ID: 22009729
FE-TF-F1 fetal d 90 ovary	PubMed ID: 22009729
FE-T vs. TF-F1 fetal d 90 ovary	PubMed ID: 22009729
FE-HCD-F0 adult female uterus	PubMed ID: 21862610
ME-HFD-F1 adult female islets	PubMed ID: 20962845
FE-VIN-F1 embryo male testis	PubMed ID: 18042343
FE-VIN-F1 embryo E13 male testis	PubMed ID: 20566332
FE-VIN-F1 embryo E14 male testis	PubMed ID: 20566332
FE-VIN-F1 embryo E16 male testis	PubMed ID: 20566332
FE-PRD-F1 adult female liver	PubMed ID: 21750721
FE-HCD-F1 embryo male blastocyst	PubMed ID: 21862610
FE-VIN-F2 embryo male testis	PubMed ID: 18042343
FE-PRD-F2 adult female liver	PubMed ID: 21750721
FE-VIN-F3 embryo male testis	PubMed ID: 18042343
FE-PRD-F3 adult female liver	PubMed ID: 21750721
FE-VIN-F3 adult male sertoli cells	PubMed ID: 23555832
FE-VIN-F3 adult female granulosa cells	PubMed ID: 22570695
FE-VIN-F3 adult female heart	PubMed ID: 23034163
FE-VIN-F3 adult female kidney	PubMed ID: 23034163
FE-VIN-F3 adult female liver	PubMed ID: 23034163
FE-VIN-F3 adult female uterus	PubMed ID: 23034163
FE-VIN-F3 adult male heart	PubMed ID: 23034163
FE-VIN-F3 adult male kidney	PubMed ID: 23034163
FE-VIN-F3 adult male liver	PubMed ID: 23034163
FE-VIN-F3 adult male prostate	PubMed ID: 23034163
FE-VIN-F3 adult male seminal vesicle	PubMed ID: 23034163
FE-VIN-F3 adult female ovary	PubMed ID: 23034163

FE-VIN-F3 adult male testis	PubMed ID: 23034163
FE-VIN-F3 adult male amygdala	PubMed ID: 19015723
FE-VIN-F3 adult male hippocampus	PubMed ID: 19015723
FE-VIN-F3 adult female amygdala	PubMed ID: 19015723
FE-VIN-F3 adult female hippocampus	PubMed ID: 19015723
FE-VIN-F3 adult male brain	PubMed ID: 19015723
FE-VIN-F3 adult male basolateral amygdala	PubMed ID: 22615374
FE-VIN-F3 adult male brain cortex	PubMed ID: 22615374
FE-VIN-F3 adult male hippocampus CA1	PubMed ID: 22615374
FE-VIN-F3 adult male hippocampus CA3	PubMed ID: 22615374
FE-VIN-F3 adult female basolateral amygdala	PubMed ID: 22615374
FE-VIN-F3 adult female brain cortex	PubMed ID: 22615374
FE-VIN-F3 adult female hippocampus CA1	PubMed ID: 22615374
FE-VIN-F3 adult female hippocampus CA3	PubMed ID: 22615374
FE-VIN-F3 adult male ventral prostate	PubMed ID: 18220299
FE-VIN-F3 adult male prostate epithelial cells	PubMed ID: 18220299
FE-VIN-F3 embryo E13 male primordial germ cells	PubMed ID: 23869203
FE-VIN-F3 embryo E16 male prospermatogonia	PubMed ID: 23869203
F0 female vinclozolin_F3 male sertoli cell DMRs	PubMed ID: 23555832
F0 female vinclozolin_F3 sperm DMRs	PubMed ID: 20927350
F0 female methoxychlor_F3 male sperm DMRs	PubMed ID: 25057798
F0 female VIN_G1 male germ cell DMRs	PubMed ID: 25853433
F0 female VIN_G2 male germ cell DMRs	PubMed ID: 25853433
F0 female VIN_G1 sperm DMRs	PubMed ID: 25853433
F0 female VIN_G2 sperm DMRs	PubMed ID: 25853433
F0 female DEPH_G1 male germ cell DMRs	PubMed ID: 25853433
F0 female DEPH_G2 male germ cell DMRs	PubMed ID: 25853433
F0 female BPA_G1 male germ cell DMRs	PubMed ID: 25853433
F0 female BPA_G2 male germ cell DMRs	PubMed ID: 25853433
F0 female EE_F1 liver hypermethylated promoters	PubMed ID: 25853433
F0 female EE_F1 liver hypomethylated promoters	PubMed ID: 25853433
F0 female EE_F1 liver hypermethylated CGI	PubMed ID: 25853433
F0 female EE_F1 liver hypomethylated CGI	PubMed ID: 25853433
Imprinted (Human)	http://www.geneimprint.com/
Predicted (Human)	http://www.geneimprint.com/
Not imprinted (Human)	http://www.geneimprint.com/
Imprinted (Mouse)	http://www.geneimprint.com/
Predicted (Mouse)	http://www.geneimprint.com/
Not imprinted (Mouse)	http://www.geneimprint.com/
Imprinted (Rat)	http://www.geneimprint.com/
mRNA (Human)	http://ctdbase.org/

protein (Human)	http://ctdbase.org/
mRNA (Mouse)	http://ctdbase.org/
protein (Mouse)	http://ctdbase.org/
mRNA (Rat)	http://ctdbase.org/
protein (Rat)	http://ctdbase.org/
Highly expressed in sperm	PubMed ID: 23471003
Expressed in oocytes	PubMed ID: 23892778
Maternal, degraded during development	http://dbtmee.hgc.jp/
Activated by minor wave of ZGA	http://dbtmee.hgc.jp/
Activated by major wave of ZGA	http://dbtmee.hgc.jp/
Transiently activated at 1-cell stage	http://dbtmee.hgc.jp/
Transiently activated at 2-cell stage	http://dbtmee.hgc.jp/
Activated by mid-preimplantation gene activation	http://dbtmee.hgc.jp/
Expressed in 4-cell stage	PubMed ID: 23892778
Expressed in 8-cell	PubMed ID: 23892778
Expressed in morula	PubMed ID: 23892778
Sperm methylation level > 50% (mouse)	PubMed ID: 21706000
Sperm methylation level < 50% (mouse)	PubMed ID: 21706000
Oocyte d5 methylation level > 50% (mouse)	PubMed ID: 21706000
Oocyte d5 methylation level < 50% (mouse)	PubMed ID: 21706000
Germinal vesicle d20 methylation level > 50% (mouse)	PubMed ID: 21706000
Germinal vesicle d20 methylation level < 50% (mouse)	PubMed ID: 21706000
Ovulated metaphase II oocyte methylation level > 50% (mouse)	PubMed ID: 21706000
Ovulated metaphase II oocyte methylation level < 50% (mouse)	PubMed ID: 21706000
Blastocyst methylation level > 50% (mouse)	PubMed ID: 21706000
Blastocyst methylation level < 50% (mouse)	PubMed ID: 21706000
Oocyte methylation level > 50% (human)	PubMed ID: 25501653
Oocyte methylation level < 50% (human)	PubMed ID: 25501653
Oocyte methylation level > 50% (mouse)	PubMed ID: 25501653
Oocyte methylation level < 50% (mouse)	PubMed ID: 25501653
H3k4me3 positive (USA)	PubMed ID: 19525931
H3k4me2 positive (USA)	PubMed ID: 19525931
H3k27me3 positive (USA)	PubMed ID: 19525931
H3K4me2 positive (Netherlands)	PubMed ID: 20473313
H3K27me3 positive (Netherlands)	PubMed ID: 20473313
H3K4me2 & H3K27me3 positive (Netherlands)	PubMed ID: 20473313
H3K4me2 & H3K27me3 negative (Netherlands)	PubMed ID: 20473313
H3K27me3 positive	PubMed ID: 23727241
H3K4me3 positive	PubMed ID: 23727241

H3K27me3 & H3K4me3 positive	PubMed ID: 23727241
H3K27me3 & H3K4me3 negative	PubMed ID: 23727241
H3K27me3 positive	PubMed ID: 23727241
H3K4me3 positive	PubMed ID: 23727241
H3K27me3 & H3K4me3 positive	PubMed ID: 23727241
H3K27me3 & H3K4me3 negative	PubMed ID: 23727241
Expressed in all tissues	PubMed ID: 25613900
Tissue enriched	PubMed ID: 25613900
Group enriched	PubMed ID: 25613900
Tissue enhanced	PubMed ID: 25613900
Total proteins	PubMed ID: 25613900
Low CpG promoters	PubMed ID: 17334365
Intermediate CpG promoters	PubMed ID: 17334365
High CpG promoters	PubMed ID: 17334365
All cell/tissue types	PubMed ID: 25693566
Cell/tissue types excluding ESCs	PubMed ID: 25693566

Table S6

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Table S7. Data source used in the analysis shown in Fig. 3.

<i>Figure label</i>	<i>Data source</i>
LCP	PubMed ID: 22016335
HCP	PubMed ID: 22016335
NHGRI	https://www.genome.gov/
GAD	http://geneticassociationdb.nih.gov/
MIM	http://www.omim.org/
LSDB	http://geneticassociationdb.nih.gov/
CTD	http://ctdbase.org/

Table S8

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