Supplementary Notes

Genetic regulation of methylation in human endometrium and blood and gene targets for reproductive diseases

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Supplementary Note 1:

Thirty-five per cent (155,675) of the DNAm probe sites in endometrial samples were hypomethylated ($\beta<0.2$) in at least 90% of samples irrespective of menstrual cycle stage or endometriosis status and 22% (97,145) of the DNAm probe sites were consistently hypermethylated ($\beta>0.8$) (Figure 1A). The proportions and distributions of hypomethylated and hypermethylated sites was similar in blood sample DNA, with 37% (161,747) of the DNAm probe sites in blood DNA consistently hypomethylated and 33% (146,090) of the DNAm probe sites consistently hypermethylated (Figure 1A).

Cpg islands were defined as regions >500bp in length with > 5% GC sequence and an expected/observed CpG ratio of >0.65, shores were defined as regions 2kb upstream/downstream from CpG islands, shelves as regions between 2 and 4 kb from CpG islands and finally all remaining regions were defined as open sea.

Hypomethylated sites were more common in CpG islands (65%) compared to open sea regions (9%) (Figure 1B). The opposite was observed for hypermethylated sites which were more common in open sea regions (54%) than CpG islands (12%) (Figure 1B). Approximately 65% of hypomethylated sites in blood were located in CpG islands, 10% where in open sea regions, and 55% of hypermethylated sites in blood were in open sea regions and only 10% were in CpG islands (Figure 1C).

Supplementary Note 2:

The majority of loci (58%) from the M2T analysis show opposite directions of effect. For alleles increasing methylation at specific sites, gene expression decreases and vice versa. The remaining 42% of eQTL and mQTL associations had allelic effects in the same direction. Similarly, 65% of T2M associations had effects in the opposite direction.

Supplementary Note 3:

mQTL DNAm probes were also annotated to predicted regulatory regions, the majority were in promoters (27.7%), 15.5% in enhancers and 24% were in quiescent regions in endometrium, and similarly, 28.6% were in promoters, 15.5% in enhancers and 21.8% were in quiescent regions in blood.