| MRE restriction enzyme | 4mer CpG context | Instances in mm9 genome (1 strand) |
|------------------------|------------------|-----------------------------------|
|                        | ACGT             | 1,756,359                         |
| HpaII*                 | CCGG             | 1,594,148                         |
|                        | CCGT             | 1,454,486                         |
|                        | ACGG             | 1,449,336                         |
|                        | TCGG             | 1,404,375                         |
|                        | CCGA             | 1,401,476                         |
|                        | TCGT             | 1,392,167                         |
|                        | TCGA             | 1,391,828                         |
|                        | ACGA             | 1,391,206                         |
|                        | GCGT             | 1,258,753                         |
|                        | ACGC             | 1,255,903                         |
| AciI                   | CCGC             | 1,251,553                         |
|                        | GCGG             | 1,250,525                         |
| Hin6I                  | GCGC             | 1,102,589                         |
|                        | TCGC             | 995,280                           |
|                        | GCGA             | 992,773                           |
|                        | NCGA             | 7                                 |
|                        | NCGC             | 4                                 |
|                        | ACGN             | 3                                 |
|                        | CCGN             | 3                                 |
|                        | GCGN             | 2                                 |
|                        | NCGG             | 2                                 |
|                        | NCGT             | 1                                 |
| **Total**              | **21,342,779**   |                                   |

Supplementary Table A
|                | Total Mapped Reads | Mean CpG coverage depth |
|----------------|--------------------|-------------------------|
| WGBS EARLY     | 429,374,384        | 7.80                    |
| WGBS ESC       | 391,724,853        | 7.23                    |
| RRBS EARLY     | 12,826,209         | 12.49                   |
| RRBS ESC       | 18,131,716         | 18.88                   |
| MREBS EARLY Rep1 | 11,963,716       | 5.72                    |
| MREBS EARLY Rep2 | 12,400,629       | 5.78                    |
| MREBS ESC Rep1 | 11,835,343         | 6.35                    |
| MREBS ESC Rep2 | 12,222,192         | 6.28                    |

Supplementary Table B
| Method              | CpG dimers* | %     |
|---------------------|-------------|-------|
| WGBS EARLY DNAme    | 17,202,917  | 80.6% |
| WGBS ESC DNAme      | 17,022,903  | 79.8% |
| RRBS EARLY DNAme    | 1,289,663   | 6.0%  |
| RRBS ESC DNAme      | 1,358,529   | 6.4%  |
| MREBS EARLY Rep1 DNAme | 962,559   | 4.5%  |
| MREBS EARLY Rep2 DNAme | 924,551   | 4.3%  |
| MREBS ESC Rep1 DNAme | 918,508   | 4.3%  |
| MREBS ESC Rep2 DNAme | 973,441   | 4.6%  |
| MREBS EARLY Rep1 Counts>0 | 14,695,688 | 68.9% |
| MREBS EARLY Rep2 Counts>0 | 14,718,855 | 69.0% |
| MREBS ESC Rep1 Counts>0 | 13,602,796 | 63.7% |
| MREBS ESC Rep2 Counts>0 | 13,947,144 | 65.3% |
| MREBS EARLY Rep1 Counts>=2 | 10,250,065 | 48.0% |
| MREBS EARLY Rep2 Counts>=2 | 10,315,026 | 48.3% |
| MREBS ESC Rep1 Counts>=2 | 8,987,596  | 42.1% |
| MREBS ESC Rep2 Counts>=2 | 9,227,587  | 43.2% |
| MREBS EARLY Rep1 Counts>=5 | 5,317,311  | 24.9% |
| MREBS EARLY Rep2 Counts>=5 | 5,387,683  | 25.2% |
| MREBS ESC Rep1 Counts>=5 | 4,696,304  | 22.0% |
| MREBS ESC Rep2 Counts>=5 | 4,659,571  | 21.8% |
| MREBS EARLY Rep1 Counts>=10 | 3,557,311  | 16.7% |
| MREBS EARLY Rep2 Counts>=10 | 3,610,365  | 16.9% |
| MREBS ESC Rep1 Counts>=10 | 3,389,630  | 15.9% |
| MREBS ESC Rep2 Counts>=10 | 3,352,308  | 15.7% |

Supplementary Table C
| Method         | CpG dimers with 5X coverage in both EARLY and ESC | %   |
|---------------|-----------------------------------------------|-----|
| WGBS          | 16,113,172                                    | 75.5% |
| RRBS Rep1     | 1,204,249                                      | 5.6% |
| MREBS Rep1    | 649,614                                        | 3.0% |
| MREBS Rep2    | 665,431                                        | 3.1% |

| Method         | CpG dimers with at least 2 reads in the surrounding 1 kB region in at least one sample | %   |
|---------------|------------------------------------------------------------------------------------------|-----|
| MREBS Rep1    | 12,542,720                                                                                | 58.8% |
| MREBS Rep2    | 12,746,080                                                                                | 59.7% |

Supplementary Table D
|                | Model 1 | Model 2 | Model 3 | Model 4 |
|----------------|---------|---------|---------|---------|
| RRBS-based     |         |         |         |         |
| differential   |         |         |         |         |
| DNA            |         |         |         |         |
| methylation    |         |         |         |         |
| B0 (intercept) | 5.29    | 5.09    | 4.92    | 5.45    |
|                |         |         |         | 5.01    |
| B1             | 0.75    | 0.53    | 0.54    | 0.63    |
| B2             | N/A     | -0.09   | -0.09   | N/A     |

Supplementary Table E