

**Figure S1** Heatmaps of *P*-values and rejection regions (those with *P*-values  $\leq 0.05$ ; shaded in black): (a) Storer–Kim (SK); (b) Fisher's exact (FE); and (c) and chi-squared (CS) tests. The results are for a pair of p's fixed at  $p_1 = 0.6$  and  $p_2 = 0.4$ . For each method, the rejection region is the combination of  $(n_1, n_2)$  (in the range of 1-100) for which the DMC is declared. Note that the jagged line in (b) is due to the discrete nature of the FE test.



**Figure S2** Heatmaps of *P*-values and rejection regions (those with *P*-values  $\leq 0.05$ ; shaded in black): (a) Storer–Kim (SK); (b) Fisher's exact (FE); and (c) and chi-squared (CS) tests. The results are for a pair of p's fixed at  $p_1 = 0.75$  and  $p_2 = 0.25$ . For each method, the rejection region is the combination of  $(n_1, n_2)$  (in the range of 1-100) for which the DMC is declared. Note that the jagged line in (b) is due to the discrete nature of the FE test.



**Figure S3** Heatmaps of *P*-values and rejection regions (those with *P*-values  $\leq 0.05$ ; shaded in black): (a) Storer–Kim (SK); (b) Fisher's exact (FE); and (c) and chi-squared (CS) tests. The results are for a pair of p's fixed at  $p_1 = 0.8$  and  $p_2 = 0.6$ . For each method, the rejection region is the combinations of  $(n_1, n_2)$  (in the range of 1-100) for which DMC is declared. Note that the jagged line in (b) is due to the discrete nature of the FE test.



**Figure S4** Heatmaps of *P*-values and rejection regions (those with *P*-values  $\leq 0.05$ ; shaded in black): (a) Storer–Kim (SK); (b) Fisher's exact (FE); and (c) and chi-squared (CS) tests. The results are for a scenario in which the total number of reads is 50 in both samples. For each method, the rejection region is the combination of  $(p_1, p_2)$  (in the range of 0-1) for which the DMC is declared. Note that the jagged line in (b) is due to the discrete nature of the FE test.



**Figure S5** Heatmaps of *P*-values and rejection regions (those with *P*-values  $\leq 0.05$ ; shaded in black): (a) Storer–Kim (SK); (b) Fisher's exact (FE); and (c) and chi-squared (CS) tests. The results are for a scenario in which the total numbers of reads are 40 and 10 in the two samples. For each method, the rejection region is the combination of  $(p_1, p_2)$  (in the range of 0-1) for which the DMC is declared. Note that the jagged line in (b) is due to the discrete nature of the FE test.



**Figure S6** Heatmaps of *P*-values and rejection regions (those with *P*-values  $\leq 0.05$ ; shaded in black): (a) Storer–Kim (SK); (b) Fisher's exact (FE); and (c) and chi-squared (CS) tests. The results are for a scenario in which the total numbers of reads are 80 and 20 in the two samples. For each method, the rejection region is the combination of  $(p_1, p_2)$  (in the range of 0-1) for which the DMC is declared. Note that the jagged line in (b) is due to the discrete nature of the FE test.



**Figure S7** Venn diagrams of numbers of DMCs detected by three methods chromosome-by-chromosome. Note that a site is designated a DMC if the chromosome-wise FDR  $\leq$  0.05.



**Figure S8** Histogram of the read counts for chromosomes 1–22, X, and Y from the H1 (top) and I90 (bottom) cell lines.



**Figure S9** Venn diagram of the numbers of DMCs detected by three classical methods, FE, CS, SK, and a newer method, MOABS. For the classical methods, a site is designated a DMC if FDR  $\leq$  0.05. For MOABS, a site is designated a DMC if its credible methylation difference (CDIF) is greater than 0.2, a threshold suggested in the software.