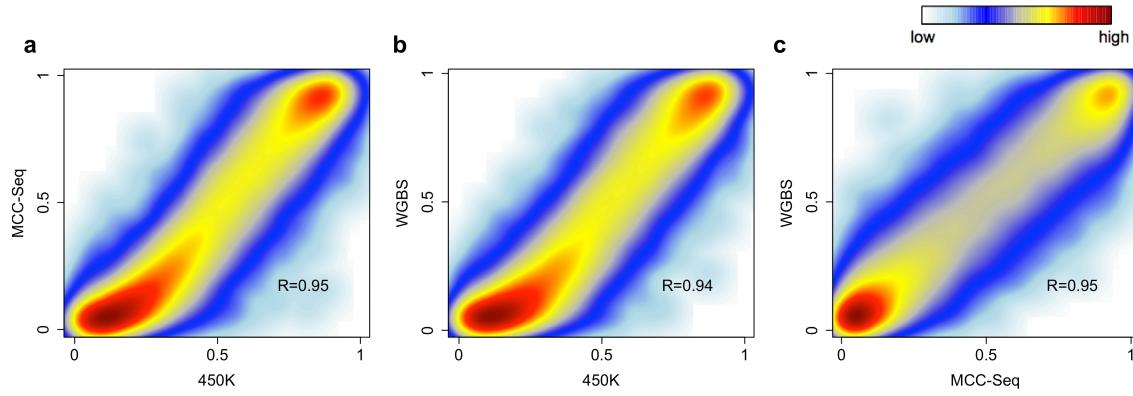
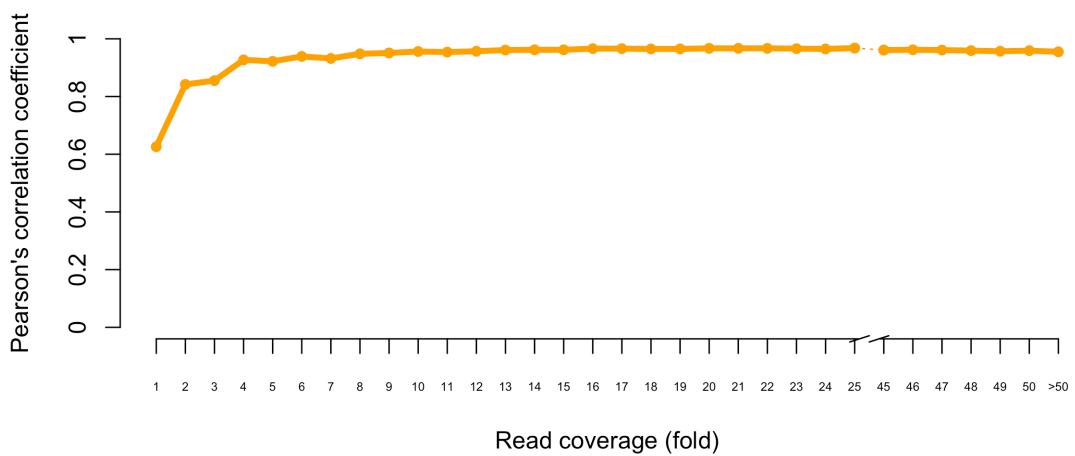


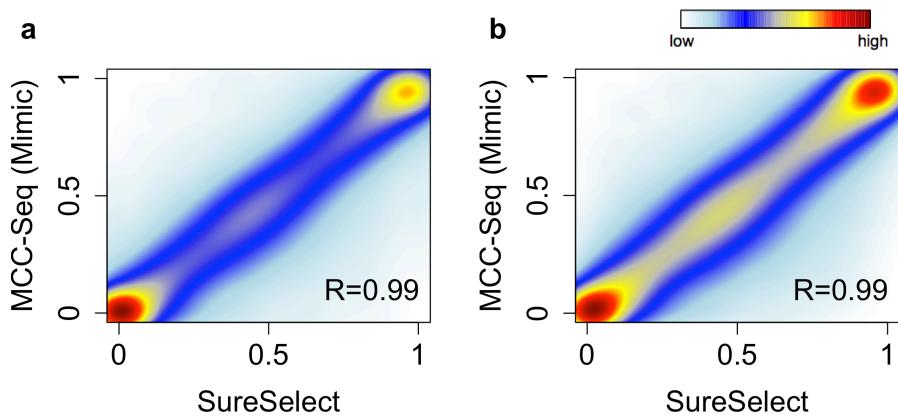
## Supplementary Figures



**Supplementary Figure 1. Extended comparison of MCC-Seq methylation calls with WGBS and the Illumina 450K array excluding completely hypo and hypermethylated CpGs** (a) Correlation between MCC-Seq<sub>4-plex</sub> and Illumina 450K array methylation calls for the same VAT DNA sample ( $R=0.95$ ), (b) comparison between WGBS and Illumina 450K array results ( $R=0.94$ ) and (c) comparison between WGBS and MCC-Seq<sub>4-plex</sub> results ( $R=0.95$ ). Only CpGs with data available from all three techniques were included as well as excluding completely hypo and hypermethylated CpGs ( $N=150,898$  CpGs); we required sequence coverage  $\geq 5X$  for MCC-Seq and WGBS;  $R$  is the Pearson correlation coefficient.

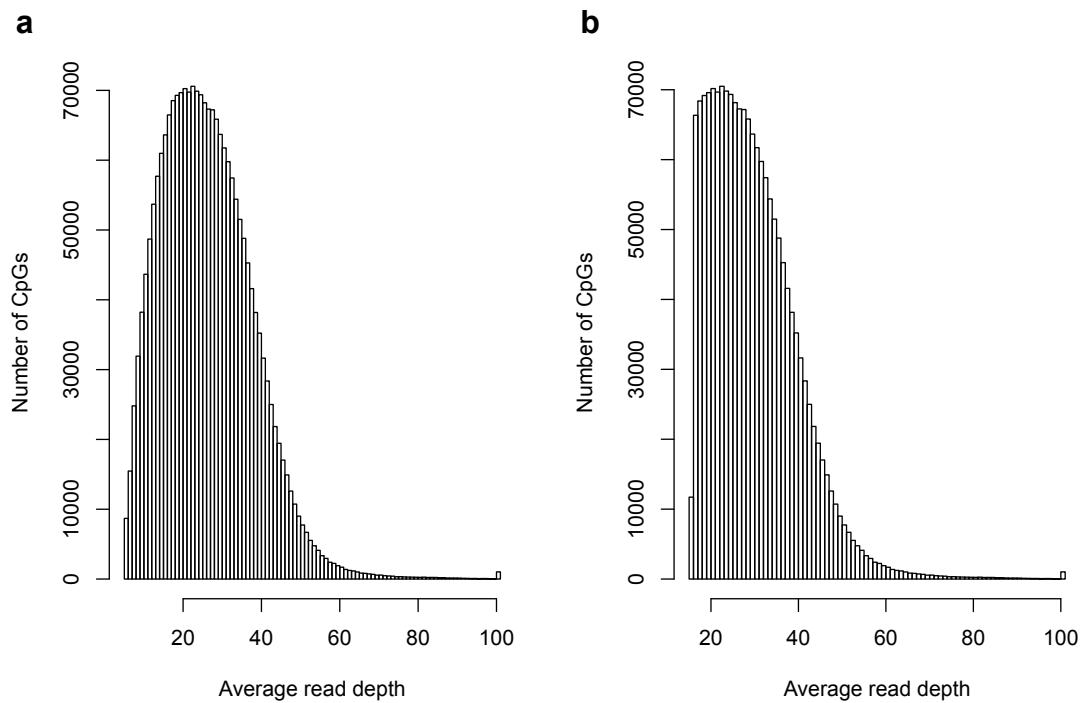


**Supplementary Figure 2. Correlation between Illumina 450K array and MCC-Seq methylation calls at different read coverage** Pearson correlation between Illumina 450K array and MCC-Seq methylation calls for the same VAT DNA sample is shown at different read depth (fold, x-axis).



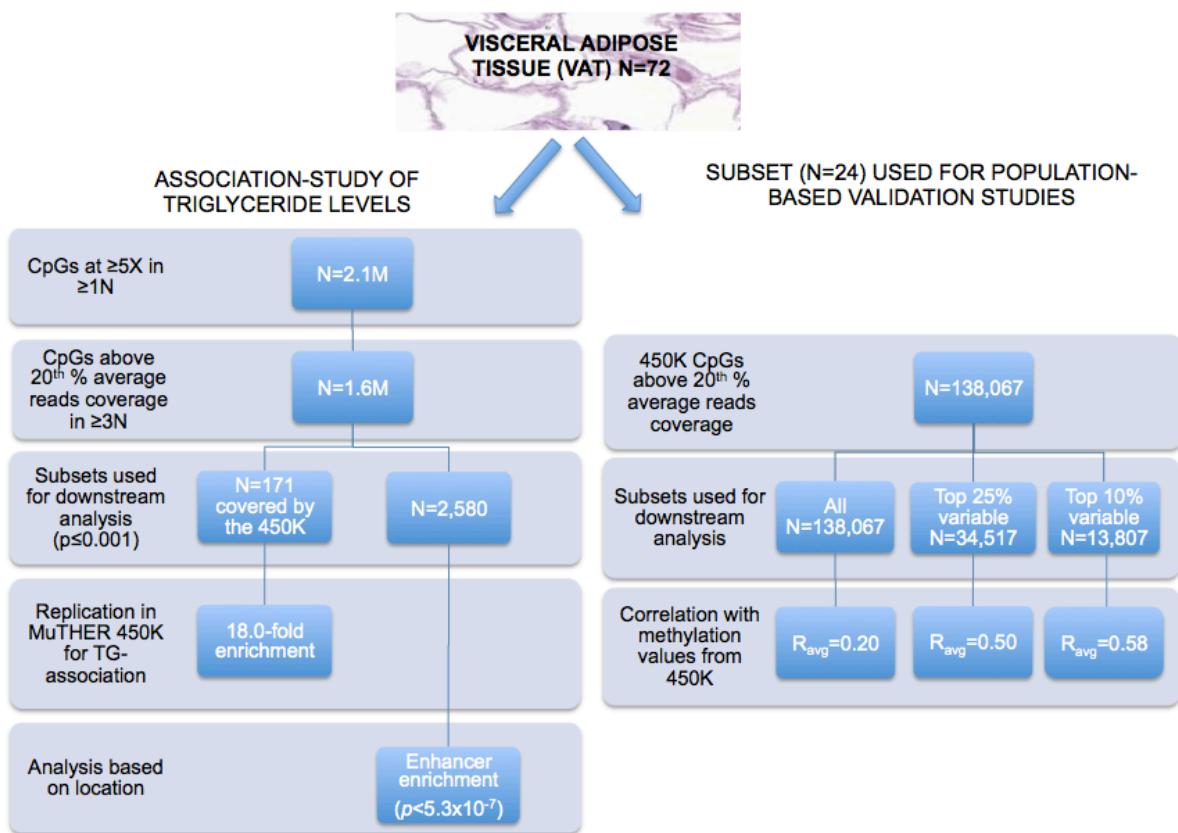
**Supplementary Figure 3. Comparison of MCC-Seq methylation calls with Agilent SureSelect**

Correlations between MCC-Seq<sub>Mimic</sub> and Agilent SureSelect methylation calls for the LCL GM12878 cell line (**a**) using all overlapping CpGs (N=2,551,186; R=0.99) and (**b**) excluding hypo (0%) and hypermethylated CpGs (N=1,734,371; R=0.99). Only CpGs with data available from both techniques were included; we required sequence coverage  $\geq 5X$  for MCC-Seq and WGBS accordingly; R is the Pearson correlation coefficient; density scales are independent in the two panels.

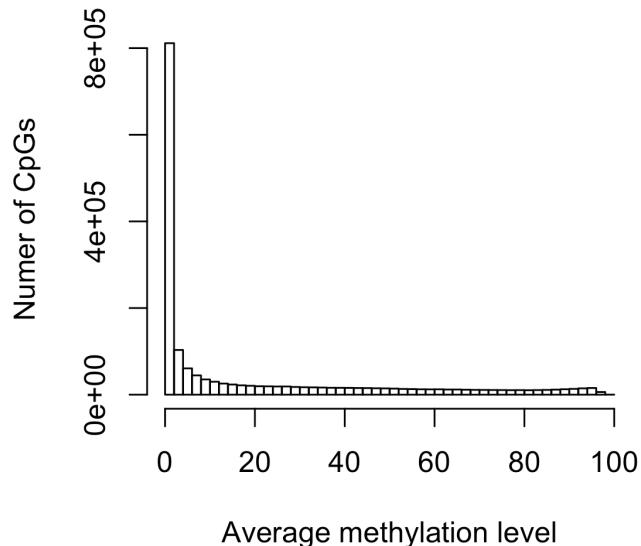


#### Supplementary Figure 4. Distributions of sequence coverage at included CpG sites

Distributions of the average read depth across the 72 individuals of included CpG sites when considering (a) all CpG sites with  $\geq 5X$  and  $\leq 100X$  sequence depth and (b) sites meeting these criteria and with average sequence depth above the 20<sup>th</sup> percentile.

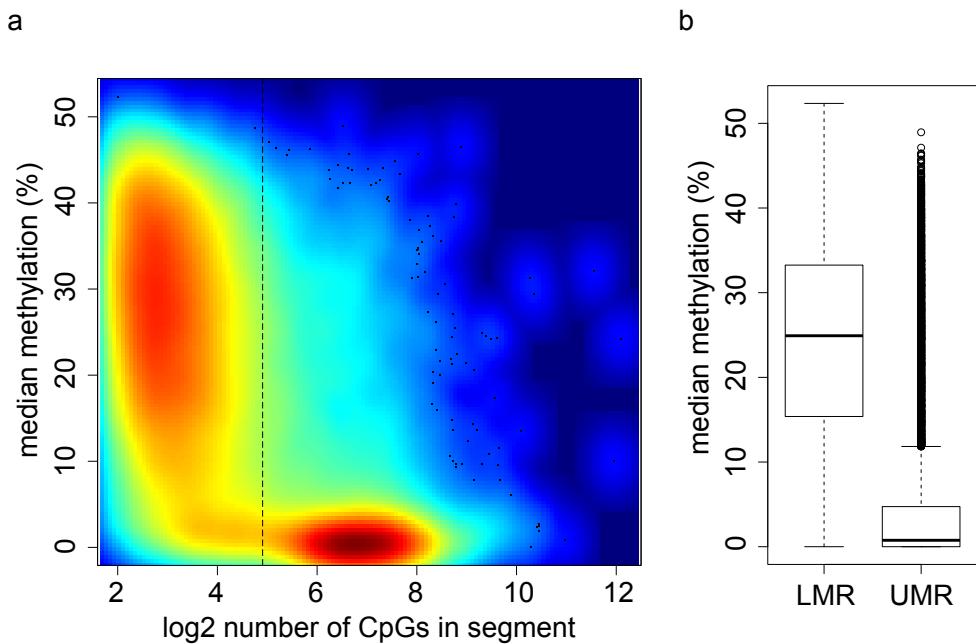


**Supplementary Figure 5. Outline of the trait association and population-based validation studies** In the left panel, an outline of the subsets used for different analysis in the association-study of methylation to triglyceride levels as well as main results are presented. In the right panel, the outline of the population-based validation studies comparing methylation values obtained with the 450K array and MCC-Seq in 24 individuals is shown.



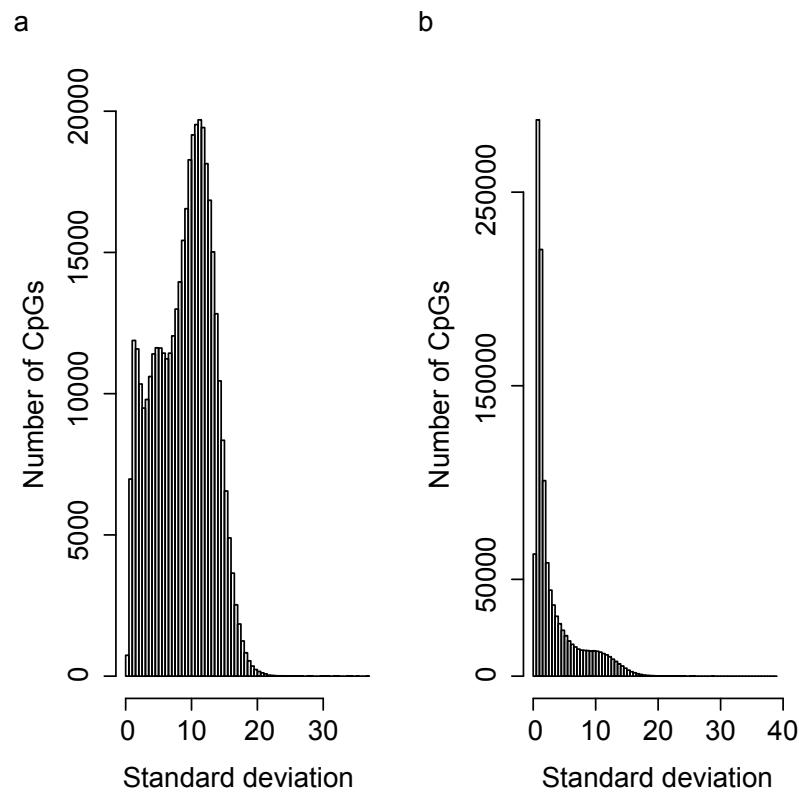
**Supplementary Figure 6. Average methylation pattern of CpGs captured with MCC-**

**Seq Met V1 design** The figure shows the average methylation values (%), x-axis for 72 visceral adipose tissue samples at on-target CpG sites above the 20<sup>th</sup> percentile average reads coverage (N=1,710,209) from Met V1 capture experiments.



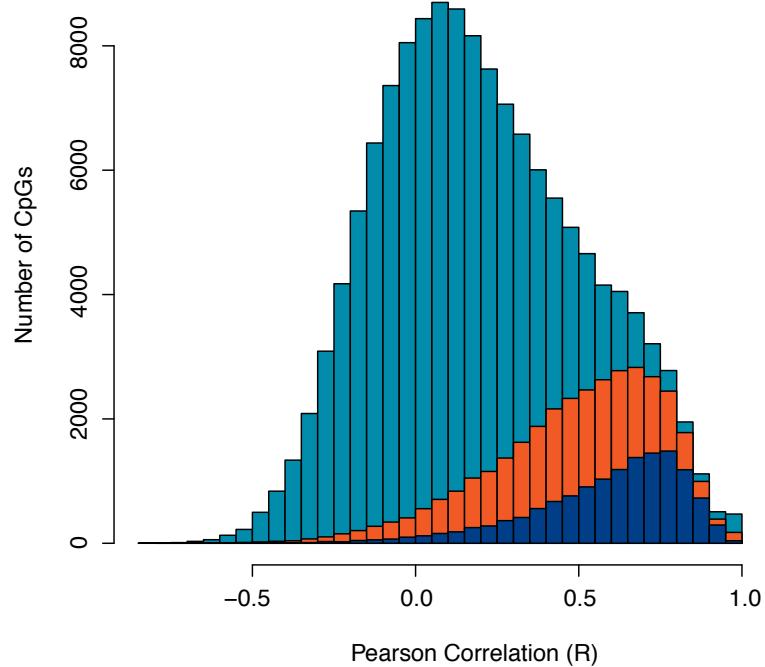
### Supplementary Figure 7. Characterization of adipose hypomethylated footprints

Hypomethylated footprints were generated from WGBS on AT using the R/Bioconductor package MethylSeekR. **(a)** Unmethylated regions (UMRs, right of dotted line) and low-methylated regions (LMRs, left of dotted line) were differentiated by a 30 CpG content threshold. **(b)** LMRs ( $N=45,065$ ) and UMRs ( $N=20,195$ ) show different median methylation patterns with LMRs having a broader range of methylation and UMRs being less variable in their methylation status and associated to low-methylated promoter regions. Boxplot whiskers represent  $1.5 \times \text{IQR}$  (inter quartile range).

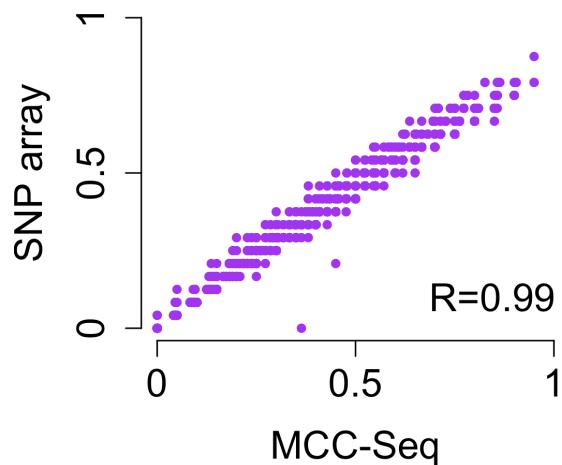


### Supplementary Figure 8. Variability of enhancer and promoter associated CpG sites

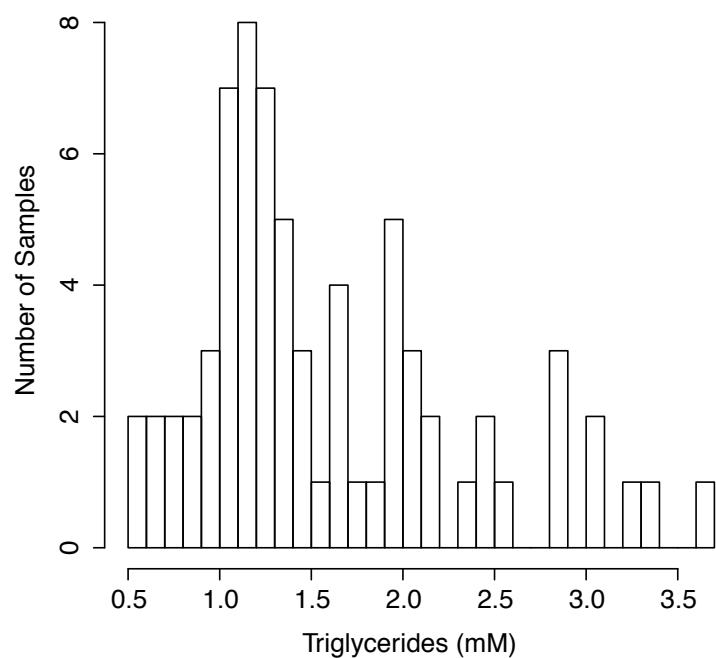
Interrogated CpG sites were mapped to putative enhancers (H3K4me1 or LMR) or promoters (H3K4me3 and UMR). Assessing the standard deviation of the methylation status across individuals **(a)** CpGs mapping to putative enhancers were found to be more variable (median SD=9.4) than **(b)** those mapping to putative promoters (median SD=1.5).



**Supplementary Figure 9. CpG-by-CpG correlation between Illumina 450K array and MCC-Seq methylation calls in 24 samples** The figure shows the distribution of spearman rank correlations for CpGs from the Illumina 450K array that had average reads coverage above the 20<sup>th</sup> percentile in the MCC-Seq method (teal; N=138,067 CpGs; mean R =0.20). The correlations were generally greater when we included only the top 25% variable CpGs (orange; N=34,517 CpGs; mean R=0.50) or the top 10% variable CpGs (blue; N=13,807 CpGs; mean R=0.58) from the MCC-Seq methylation calls.



**Supplementary Figure 10. Comparison of the observed heterozygosity from MCC-Seq and HumanOmni BeadChip array genotyping calls** Comparison between the observed heterozygosity based on the HumanOmni BeadChip array (SNP ratio, y-axis) and MCC-Seq<sub>plex</sub> (SNP ratio, x-axis) genotyping calls across ≥20 individuals (N=3,093 SNPs; R=0.99); we required sequence coverage ≥5X for MCC-Seq; R is the Pearson correlation coefficient.



**Supplementary Figure 11. Distribution of triglycerides levels in the discovery cohort**

Distributions of the triglyceride levels (mM, x-axis) across the discovery cohort (N=70, two outliers excluded).

Supplementary Table 1. Sequence statistics of the Met V1 pooled samples

|            | Plexing level | Sample ID | raw reads   | Total aligned reads (%) | Total on-target reads (%) | Total on-target aligned reads (%) | On-target aligned reads | Average coverage on-target CpG sites | Total captured on-target CpG sites (%) | Total CpG sites with >=5 reads (%) | Total CpG sites with >=10 reads (%) |
|------------|---------------|-----------|-------------|-------------------------|---------------------------|-----------------------------------|-------------------------|--------------------------------------|--|------------------------------------|-------------------------------------|
| Individual | 1             | 1         | 257,885,682 | 60                      | 67                        | 40                                | 95,832,520              | 82                                   | 99                                     | 94                                 | 94                                  |
|            | 2             | 1         | 151,069,388 | 60                      | 71                        | 43                                | 58,871,218              | 53                                   | 99                                     | 91                                 | 90                                  |
|            | 2             | 2         | 144,059,126 | 62                      | 69                        | 43                                | 57,386,604              | 50                                   | 99                                     | 90                                 | 89                                  |
|            | 4             | 3         | 65,799,220  | 70                      | 79                        | 55                                | 35,355,720              | 33                                   | 99                                     | 82                                 | 80                                  |
|            | 4             | 4         | 62,929,502  | 72                      | 80                        | 57                                | 34,630,762              | 33                                   | 99                                     | 82                                 | 79                                  |
|            | 4             | 5         | 57,375,348  | 72                      | 79                        | 57                                | 31,638,544              | 30                                   | 99                                     | 80                                 | 77                                  |
|            | 4             | 6         | 51,172,122  | 73                      | 78                        | 57                                | 28,258,060              | 27                                   | 99                                     | 80                                 | 76                                  |
|            | 6             | 1         | 65,153,260  | 74                      | 55                        | 41                                | 26,090,152              | 24                                   | 99                                     | 80                                 | 76                                  |
|            | 6             | 2         | 51,084,062  | 76                      | 56                        | 43                                | 21,392,302              | 21                                   | 99                                     | 77                                 | 71                                  |
|            | 6             | 7         | 59,331,638  | 73                      | 55                        | 40                                | 23,132,120              | 21                                   | 99                                     | 77                                 | 71                                  |
|            | 6             | 8         | 72,222,874  | 74                      | 55                        | 41                                | 29,161,380              | 27                                   | 99                                     | 82                                 | 78                                  |
|            | 6             | 9         | 65,481,242  | 73                      | 54                        | 39                                | 25,251,428              | 24                                   | 99                                     | 80                                 | 75                                  |
|            | 6             | 10        | 71,864,932  | 72                      | 54                        | 39                                | 27,850,522              | 25                                   | 99                                     | 80                                 | 76                                  |
|            | 10            | 11        | 36,474,056  | 75                      | 59                        | 44                                | 15,739,422              | 14                                   | 98                                     | 65                                 | 54                                  |
|            | 10            | 12        | 32,548,084  | 76                      | 59                        | 45                                | 14,374,870              | 13                                   | 98                                     | 63                                 | 51                                  |
|            | 10            | 13        | 32,058,534  | 76                      | 59                        | 45                                | 14,139,984              | 13                                   | 98                                     | 62                                 | 49                                  |
|            | 10            | 14        | 29,780,130  | 75                      | 60                        | 45                                | 13,047,378              | 12                                   | 98                                     | 60                                 | 46                                  |
|            | 10            | 15        | 38,922,258  | 74                      | 58                        | 43                                | 16,445,576              | 15                                   | 98                                     | 67                                 | 56                                  |
|            | 10            | 16        | 34,623,254  | 74                      | 57                        | 42                                | 14,442,798              | 13                                   | 98                                     | 62                                 | 50                                  |
|            | 10            | 17        | 40,850,638  | 75                      | 51                        | 38                                | 15,457,642              | 14                                   | 98                                     | 66                                 | 55                                  |
|            | 10            | 18        | 28,196,414  | 74                      | 58                        | 43                                | 11,877,752              | 10                                   | 98                                     | 55                                 | 38                                  |
|            | 10            | 19        | 31,954,644  | 76                      | 60                        | 46                                | 14,209,644              | 13                                   | 98                                     | 63                                 | 50                                  |
|            | 10            | 20        | 32,427,388  | 75                      | 59                        | 44                                | 14,171,532              | 13                                   | 98                                     | 62                                 | 49                                  |
| Average    | 1             | NA        | 257,885,682 | 60                      | 67                        | 40                                | 95,832,520              | 82                                   | 99                                     | 94                                 | 94                                  |
|            | 2             | NA        | 147,564,257 | 61                      | 70                        | 43                                | 58,128,911              | 51                                   | 99                                     | 90                                 | 90                                  |
|            | 4             | NA        | 59,319,048  | 72                      | 79                        | 57                                | 31,194,649              | 31                                   | 99                                     | 81                                 | 78                                  |
|            | 6             | NA        | 64,189,668  | 74                      | 55                        | 41                                | 25,446,317              | 24                                   | 99                                     | 79                                 | 75                                  |
|            | 10            | NA        | 33,783,540  | 75                      | 58                        | 44                                | 14,390,660              | 13                                   | 98                                     | 63                                 | 50                                  |

Supplementary Table 2. Sequence statistics of the Met V2 pooled samples

|            | Plexing level | Sample ID | raw reads  | Total aligned reads (%) | Total on-target reads (%) | Total on-target aligned reads (%) | On-target aligned reads | Average coverage on-target CpG sites | Total captured on-target CpG sites (%) | Total CpG sites with >=5 reads (%) | Total CpG sites with >=10 reads (%) |
|------------|---------------|-----------|------------|-------------------------|---------------------------|-----------------------------------|-------------------------|--------------------------------------|--|------------------------------------|-------------------------------------|
| Individual | 6             | 21        | 52,965,668 | 71                      | 62                        | 44                                | 23,013,966              | 13                                   | 98                                     | 62                                 | 50                                  |
|            | 6             | 22        | 52,005,852 | 72                      | 62                        | 44                                | 22,681,612              | 13                                   | 98                                     | 62                                 | 50                                  |
|            | 6             | 23        | 76,717,544 | 73                      | 62                        | 45                                | 34,152,304              | 20                                   | 98                                     | 73                                 | 67                                  |
|            | 6             | 24        | 59,008,738 | 73                      | 61                        | 45                                | 26,098,106              | 16                                   | 98                                     | 66                                 | 64                                  |
|            | 6             | 25        | 53,915,196 | 71                      | 62                        | 44                                | 23,447,444              | 14                                   | 98                                     | 63                                 | 51                                  |
|            | 6             | 26        | 60,990,908 | 72                      | 63                        | 45                                | 27,036,892              | 16                                   | 98                                     | 67                                 | 58                                  |
|            | Average       | 6         | NA         | 59,266,984              | 72                        | 62                                | 45                      | 26,071,387                           | 15                                     | 98                                 | 65                                  |

**Supplementary Table 3. Comparison of MCC-Seq methylation calls with Illumina 450K array and WGBS data at various read depths**

| Technique comparisons | Pearson Correlation   |                        |                       |                       |
|-----------------------|-----------------------|------------------------|-----------------------|-----------------------|
|                       | >=5X (N=150,898 CpGs) | >=10X (N=144,868 CpGs) | >=20X (N=90,547 CpGs) | >=30X (N=17,852 CpGs) |
| 450K~MCC-Seq          | 0.964                 | 0.964                  | 0.965                 | 0.962                 |
| 450K~WGBS             | 0.962                 | 0.962                  | 0.961                 | 0.959                 |
| MCC-Seq~WGBS          | 0.974                 | 0.974                  | 0.974                 | 0.972                 |

**Supplementary Table 4. Comparison of MCC-Seq methylation calls with Illumina 450K array and WGBS data at various read depths excluding completely hypo and hypermethylated CpGs**

| Technique comparisons | Pearson Correlation  |                       |                       |                      |
|-----------------------|----------------------|-----------------------|-----------------------|----------------------|
|                       | >=5X (N=45,097 CpGs) | >=10X (N=44,414 CpGs) | >=20X (N=30,934 CpGs) | >=30X (N=7,182 CpGs) |
| 450K-MCC-Seq          | 0.946                | 0.947                 | 0.952                 | 0.953                |
| 450K-WGBS             | 0.942                | 0.943                 | 0.946                 | 0.947                |
| MCC-Seq-WGBS          | 0.949                | 0.950                 | 0.955                 | 0.958                |

Supplementary Table 5. MuTHER replication and cis-mQTL regulation of top TG-associated CpGs

| CpG rank | CpG chr | CpG start | CpG end   | 450K ProbeID | 450K probe start position | 450K probe end position | MuTHER Anova association p-value | MuTHER beta value | MuTHER replication status | SNP        | SNP position | MAF   | cis-mQTL p-value | cis-mQTL beta value | Gene      | cis-mQTL status at FDR 1% |
|----------|---------|-----------|-----------|--------------|---------------------------|-------------------------|----------------------------------|-------------------|---------------------------|------------|--------------|-------|------------------|---------------------|-----------|---------------------------|
| 1        | chr7    | 80276086  | 80276087  | cg05917188   | 80275870                  | 80275919                | 3.22E-07                         | 0.02160           | REPLICATED                | rs7755     | 80306271     | 0.444 | 1.52E-01         | -0.00522            | CD36      | .                         |
| 2        | chr18   | 46459491  | 46459492  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 3        | chr14   | 82002624  | 82002625  | cg25066972   | 82002568                  | 82002617                | 1.47E-08                         | 0.02701           | REPLICATED                | rs7149751  | 82042759     | 0.182 | 7.40E-04         | 0.01867             | NA        | SIGNIFICANT               |
| 4        | chr15   | 40374156  | 40374157  | cg11448015   | 40374034                  | 40374083                | 1.16E-01                         | -0.00098          |                           | rs98713    | 40378467     | 0.401 | 4.13E-02         | 0.00143             | NA        | .                         |
| 5        | chr12   | 68352059  | 68352060  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 6        | chr10   | 14791641  | 14791642  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 7        | chr17   | 78747573  | 78747574  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 8        | chr17   | 70419164  | 70419165  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 9        | chr7    | 2527288   | 2527289   | cg07446753   | 2527391                   | 2527440                 | 1.24E-06                         | 0.01593           | REPLICATED                | rs10498610 | 2606934      | 0.074 | 3.24E-04         | -0.01873            | NA        | SIGNIFICANT               |
| 10       | chr7    | 105494830 | 105494831 | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 11       | chr14   | 93499059  | 93499059  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 12       | chr11   | 11778803  | 11778804  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 13       | chr17   | 78747529  | 78747530  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 14       | chr4    | 127837946 | 127837947 | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 15       | chr15   | 91068554  | 91068555  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 16       | chr1    | 1174212   | 1174213   | cg0587094    | 1174190                   | 1174239                 | 1.37E-01                         | 0.00441           |                           | rs3813199  | 1158277      | 0.102 | 1.10E-34         | 0.05102             | NA        | SIGNIFICANT               |
| 17       | chr6    | 74276861  | 74276862  | cg04958236   | 74276973                  | 74277022                | 2.28E-01                         | -0.00369          |                           | rs4708064  | 74275405     | 0.338 | 3.56E-32         | 0.03455             | NA        | SIGNIFICANT               |
| 18       | chr9    | 34892821  | 34892822  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 19       | chr9    | 80052788  | 80052789  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 20       | chr1    | 10895564  | 10895565  | cg17480077   | 10895517                  | 10895566                | 8.17E-01                         | -0.00058          |                           | rs1292657  | 10893081     | 0.233 | 1.04E-06         | 0.01362             | NA        | SIGNIFICANT               |
| 21       | chr3    | 193988521 | 193988522 | cg16932827   | 193988639                 | 193988688               | 5.02E-08                         | 0.01964           | REPLICATED                | rs7651474  | 193943677    | 0.389 | 1.95E-02         | -0.00765            | NA        | .                         |
| 22       | chr21   | 44739256  | 44739257  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 23       | chr2    | 65576937  | 65576938  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 24       | chr17   | 41030976  | 41030977  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 25       | chr1    | 224921325 | 224921326 | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 26       | chr14   | 101985031 | 101985032 | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 27       | chr17   | 27439437  | 27439438  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 28       | chr18   | 77246010  | 77246011  | cg18935516   | 77245874                  | 77245923                | 2.08E-01                         | -0.00324          |                           | rs1562274  | 77169571     | 0.112 | 4.62E-03         | 0.01148             | NFATC1    | .                         |
| 29       | chr9    | 33104269  | 33104270  | cg13858803   | 33140269                  | 33140318                | 4.87E-05                         | 0.01299           | SUGGESTED                 | rs1013217  | 33104540     | 0.259 | 3.49E-03         | -0.00908            | B4GALT1   | .                         |
| 30       | chr10   | 88013023  | 88013024  | cg24351003   | 88013120                  | 88013259                | 8.09E-01                         | -0.00050          |                           | rs2814352  | 88013439     | 0.168 | 4.92E-05         | 0.01008             | GRID1     | SIGNIFICANT               |
| 31       | chr4    | 43864205  | 43864206  | cg06800988   | 43864094                  | 43864143                | 8.48E-02                         | -0.0079           |                           | rs4595567  | 43865337     | 0.265 | 3.26E-30         | 0.01512             | NSD1      | SIGNIFICANT               |
| 32       | chr6    | 56330105  | 56330111  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 33       | chr16   | 85158006  | 85158007  | cg11201751   | 85158047                  | 85158096                | 3.98E-08                         | 0.01938           | REPLICATED                | rs2082550  | 85164601     | 0.452 | 2.38E-06         | -0.01478            | NA        | SIGNIFICANT               |
| 34       | chr7    | 37252350  | 37252351  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 35       | chr20   | 60932998  | 60932999  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 36       | chr1    | 205228721 | 205228722 | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 37       | chr16   | 2098530   | 2098531   | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 38       | chr19   | 47129789  | 47129790  | cg04706667   | 47129637                  | 47129686                | 6.95E-05                         | 0.00737           | SUGGESTED                 | rs11083841 | 47120033     | 0.153 | 6.51E-04         | 0.00780             | PTGIR     | SIGNIFICANT               |
| 39       | chr13   | 59931088  | 59931089  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 40       | chr5    | 34496834  | 34496835  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 41       | chr16   | 57825356  | 57825357  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 42       | chr6    | 6656625   | 6656626   | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 43       | chr13   | 40957432  | 40957433  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 44       | chr4    | 78265455  | 78265456  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 45       | chr15   | 31695119  | 31695120  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 46       | chr4    | 2808262   | 2808263   | cg10869531   | 2808489                   | 2808538                 | 1.55E-02                         | 0.00591           |                           | rs1269392  | 2783440      | 0.162 | 2.23E-05         | -0.01478            | SH3BP2    | SIGNIFICANT               |
| 47       | chr22   | 18042778  | 18042779  | cg04460557   | 18042646                  | 18042695                | 1.36E-01                         | 0.00325           |                           | rs174351   | 18038766     | 0.323 | 1.42E-05         | -0.00909            | SLC25A18  | SIGNIFICANT               |
| 48       | chr12   | 118227823 | 118227824 | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 49       | chr16   | 88351337  | 88351338  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 50       | chr19   | 584402    | 584402    | cg26957999   | 584425                    | 5844425                 | 3.97E-01                         | 0.00171           |                           | rs3814895  | 568860       | 0.262 | 2.01E-03         | -0.00623            | NA        | .                         |
| 51       | chr9    | 13742652  | 13742653  | cg13742657   | 13742657                  | 13742682                | 3.95E-01                         | -0.00449          |                           | rs6539494  | 13742628     | 0.078 | 2.33E-02         | 0.00717             | RXRA      | .                         |
| 52       | chr2    | 20354358  | 20354359  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 53       | chr15   | 23892336  | 23892337  | cg04124555   | 23892608                  | 23892657                | 9.67E-02                         | 0.00317           |                           | rs7495382  | 23824746     | 0.222 | 6.04E-02         | 0.00412             | MAGEL2    | .                         |
| 54       | chr3    | 61720610  | 61720611  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 55       | chr7    | 148661205 | 148661206 | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 56       | chr5    | 54818087  | 54818088  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 57       | chr22   | 37678241  | 37678241  | cg19751930   | 37678222                  | 37678221                | 3.09E-02                         | -0.00441          |                           | rs6000649  | 37677490     | 0.45  | 9.63E-20         | 0.01607             | CYTH4     | SIGNIFICANT               |
| 58       | chr3    | 124555885 | 124555886 | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 59       | chr7    | 27179312  | 27179313  | cg17775899   | 27179378                  | 27179427                | 4.18E-02                         | 0.00449           | SUGGESTED                 | rs3757640  | 27182245     | 0.255 | 7.36E-03         | 0.00660             | NA        | .                         |
| 60       | chr17   | 77404010  | 77404011  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 61       | chr2    | 38387408  | 38387409  | cg10481134   | 38387395                  | 38387444                | 7.48E-05                         | 0.01214           | SUGGESTED                 | rs4670835  | 38469162     | 0.156 | 6.05E-04         | 0.01211             | CYP1B1-AS | SIGNIFICANT               |
| 62       | chr5    | 141564812 | 141564813 | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 63       | chr5    | 31213788  | 31213789  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 64       | chr3    | 38765465  | 38765466  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 65       | chr7    | 30954512  | 30954513  | cg03310518   | 30954474                  | 30954523                | 1.87E-02                         | -0.00668          |                           | rs10225302 | 31001075     | 0.348 | 7.73E-02         | -0.00558            | AQP1      | .                         |
| 66       | chr22   | 33105136  | 33105137  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 67       | chr23   | 233764015 | 233764016 | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 68       | chr2    | 76895256  | 76895257  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 69       | chr22   | 45947785  | 45947786  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 70       | chr13   | 40957443  | 40957444  | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 71       | chr6    | 166263737 | 166263738 | cg06738040   | 166263737                 | 166263766               | 7.83E-05                         | -0.01385          | SUGGESTED                 | rs9348049  | 166263379    | 0.426 | 2.8E-04          | -0.01104            | NA        | SIGNIFICANT               |
| 72       | chr15   | 313406474 | 313406474 | NA           | NA                        | NA                      |                                  | NA                | NA                        | NA         | NA           | NA    |                  | NA                  | NA        |                           |
| 73       | chr10   | 13746428  | 13746429  | cg0269168    | 13746481                  | 13746530                | 7.20E-07                         | 0.01879           | SUGGESTED                 | rs4719344  | 13746575     | 0.226 | 1.38E-05         | 0.00693             | EBF3      | .                         |
| 74       | chr1    | 21619101  | 21619102  | cg13170600   | 216191815                 | 21619184                | 4.03E-03                         | 0.00580           | SUGGESTED                 | rs12032914 | 2161973      | 0.222 | 8.86E-06         | -0.00900            | NA        | SIGNIFICANT               |
| 75       | chr8    | 142309650 | 142309660 | cg10095414   | 142309604                 | 142309653               | 2.03E-06                         | 0.01473           | REPLICATED                | rs11781174 | 142297744    | 0.337 | 2.51E-02         | 0.00688             | NA        | .                         |
| 76       | chr9    | 34559411  | 34559412  | NA           | NA                        | NA</                    |                                  |                   |                           |            |              |       |                  |                     |           |                           |

**Supplementary Table 6. ATAC-Seq PCR amplification primers**

| ID     | Adaptor Sequence | Primer Sequence   |
|--------|------------------|---|
| Ad1    | n/a              | AATGATA CGGC GACC ACCGAGATCTACACTCGTCGGCAGCGTCAGATGTG   |
| Ad2.1  | TAAGCGA          | CAAGCAGAAGACGGCATACGAGATT CGCCTTAGTCTCGTGGGCTCGGAGATGT  |
| Ad2.2  | CGTACTAG         | CAAGCAGAAGACGGCATACGAGATCTAGTACGGTCTCGTGGGCTCGGAGATGT   |
| Ad2.3  | AGGCAGAA         | CAAGCAGAAGACGGCATACGAGATT CTGCCTGTCTCGTGGGCTCGGAGATGT   |
| Ad2.4  | TCCTGAGC         | CAAGCAGAAGACGGCATACGAGATGCTCAGGAGTCTCGTGGGCTCGGAGATGT   |
| Ad2.5  | GGACTCCT         | CAAGCAGAAGACGGCATACGAGATAGGAGTCCGTCGTGGGCTCGGAGATGT     |
| Ad2.6  | TAGGCATG         | CAAGCAGAAGACGGCATACGAGATCATGCCTAGTCTCGTGGGCTCGGAGATGT   |
| Ad2.7  | CTCTCTAC         | CAAGCAGAAGACGGCATACGAGATGTAGAGAGGTCTCGTGGGCTCGGAGATGT   |
| Ad2.8  | CAGAGAGG         | CAAGCAGAAGACGGCATACGAGATCCTCTGGTCTCGTGGGCTCGGAGATGT     |
| Ad2.9  | GCTACGCT         | CAAGCAGAAGACGGCATACGAGATAGCGTAGCGTCGTGGGCTCGGAGATGT     |
| Ad2.10 | CGAGGCTG         | CAAGCAGAAGACGGCATACGAGATCAGCCTCGGTCTCGTGGGCTCGGAGATGT   |
| Ad2.11 | AAGAGGCA         | CAAGCAGAAGACGGCATACGAGATTGCCCTTGCTCGTGGGCTCGGAGATGT     |
| Ad2.12 | GTAGAGGA         | CAAGCAGAAGACGGCATACGAGATT CCTCTACGTCTCGTGGGCTCGGAGATGT  |
| Ad2.13 | GTCGTGAT         | CAAGCAGAAGACGGCATACGAGATATCACGACGTCTCGTGGGCTCGGAGATGT   |
| Ad2.14 | ACCACTGT         | CAAGCAGAAGACGGCATACGAGATA CGAGTCTCGTGGGCTCGGAGATGT      |
| Ad2.15 | TGGATCTG         | CAAGCAGAAGACGGCATACGAGATCAGATCCAGTCTCGTGGGCTCGGAGATGT   |
| Ad2.16 | CCGTTTGT         | CAAGCAGAAGACGGCATACGAGATA CAAACGGGCTCGTGGGCTCGGAGATGT   |
| Ad2.17 | TGCTGGGT         | CAAGCAGAAGACGGCATACGAGATACCACGAGTCTCGTGGGCTCGGAGATGT    |
| Ad2.18 | GAGGGGTT         | CAAGCAGAAGACGGCATACGAGATAACCCCTCGTCTCGTGGGCTCGGAGATGT   |
| Ad2.19 | AGGTTGGG         | CAAGCAGAAGACGGCATACGAGATCCAACCTGTCGTGGGCTCGGAGATGT      |
| Ad2.20 | GTGTGGTG         | CAAGCAGAAGACGGCATACGAGATCACCACACGTCTCGTGGGCTCGGAGATGT   |
| Ad2.21 | TGGTTTTC         | CAAGCAGAAGACGGCATACGAGATGAAACCCAGTCTCGTGGGCTCGGAGATGT   |
| Ad2.22 | TGGTCACA         | CAAGCAGAAGACGGCATACGAGATT GTGACCA GTCTCGTGGGCTCGGAGATGT |
| Ad2.23 | TTGACCCCT        | CAAGCAGAAGACGGCATACGAGATAGGGTCAAGTCTCGTGGGCTCGGAGATGT   |
| Ad2.24 | CCACTCCT         | CAAGCAGAAGACGGCATACGAGATAGGAGTGGGTCTCGTGGGCTCGGAGATGT   |

**Supplementary Table 7. ATAC-Seq Q-PCR primers**

| ID          | Sequence               |
|-------------|------------------------|
| Mit_+ve_F   | CTAAATAGCCCACACGTTCCC  |
| Mit_+ve_R   | AGAGCTCCCGTGAGTGGTTA   |
| GAPDH_+ve_F | CTGTCCCTTCAGTAGCTGCC   |
| GAPDH_+ve_R | GAAGAGAGTGGGTTGGTGGG   |
| GAPDH_-ve_F | TCTGGATGGCCTGAAGGAGA   |
| GAPDH_-ve_R | GCCAGCAGCACTCATGTTTC   |
| ACTB_+ve_F  | GAGTCCTTAGGCCGCCAG     |
| ACTB_+ve_R  | TCCGACCAGTGTTCAGTGCAGA |
| ACTB_-ve_F  | CATCTCGTGTCCAGTGCAGA   |
| ACTB_-ve_R  | CCATGCAATGTGGGAGTCCT   |