

Description of Additional Supplementary Files

Title: Supplementary Data 1

Description: List of all 197,765 brain 5hmC regions (DLPFC) detected by hMe-Seal in ROSMAP

Title: Supplementary Data 2

Description: Elastic net (EN) selected 5hmC regions (>60 times over 100 runs) associated with neuropathological AD diagnosis

Title: Supplementary Data 3

Description: Elastic net (EN) selected 5hmC regions (>60 times over 100 runs) associated with A β load

Title: Supplementary Data 4

Description: Elastic net (EN) selected 5hmC regions (>60 times over 100 runs) associated with PHFtau tangles

Title: Supplementary Data 5

Description: List of 5hmC regions significantly associated with AD diagnosis in MAP by regression analysis

Title: Supplementary Data 6

Description: List of 5hmC regions significantly associated with A β load in MAP by regression analysis

Title: Supplementary Data 7

Description: List of 5hmC regions significantly associated with PHFtau in MAP by regression analysis

Title: Supplementary Data 8

Description: Replication of 5hmC regions associated with pathological diagnosis of AD in ROS

Title: Supplementary Data 9

Description: Replication of 5hmC regions associated with A β load in ROS

Title: Supplementary Data 10

Description: Replication of 5hmC regions associated with PHFtau tangles in ROS

Title: Supplementary Data 11

Description: List of 93 DhMRs associated with all three pathological phenotypes (AD diagnosis, A β load and PHFtau) in both cohorts (FDR<0.05)

Title: Supplementary Data 12

Description: List of 43 DhMRs (associated with AD diagnosis, A β load or PHFtau) that are located in regions harboring known AD GWAS loci

Title: Supplementary Data 13

Description: Association between 5hmC regions and AD pathology after additionally adjusting for genotype of the lead SNP in the candidate regions

Title: Supplementary Data 14

Description: Associations of DhMRs on chromosome 19 after adjusting for the lead SNP genotype in the candidate regions and APOE genotype

Title: Supplementary Data 15

Description: Variance (%) in AD pathologies explained by 5hmC

Title: Supplementary Data 16

Description: List of DhMRs associated with AD diagnosis in the meta-analysis

Title: Supplementary Data 17

Description: List of DhMRs associated with A β load in the meta-analysis

Title: Supplementary Data 18

Description: List of DhMRs associated with PHFtau tangles in the meta-analysis

Title: Supplementary Data 19

Description: List of 118 DhMRs associated with all three pathological phenotypes (AD diagnosis, A β load and PHFtau) in the meta-analysis (FDR<0.05)

Title: Supplementary Data 20

Description: Enrichment analysis of AD-associated 5hmCs based on brain (DLPFC) chromatin states defined by the NIH Roadmap Epigenomics Project

Title: Supplementary Data 21

Description: Characteristics of participants with both 5hmC and other omics data

Title: Supplementary Data 22

Description: Spearman correlation of AD-associated DhMRs with brain gene expression of same participants

Title: Supplementary Data 23

Description: Expression of AD-associated 5hmC genes is also associated with AD neuropathology

Title: Supplementary Data 24

Description: Enrichment analysis of protein-protein interaction (PPI) networks by STRING (FDR<0.05). A total of 740 genes showing both differentially hydroxymethylated and differentially expressed were included in this analysis. The whole genome was used as background.

Title: Supplementary Data 25

Description: Spearman correlation between AD diagnosis-associated 5hmC regions and H3K9ac ($\pm$ 50kb) in the brain cortex (DLPFC) of same subjects in ROSMAP. Only the most significant H3K9ac peaks located within 50kb to 5hmC are listed.

Title: Supplementary Data 26

Description: Spearman correlation between A β -associated 5hmC regions and H3K9ac ($\pm$ 50kb) in the brain cortex (DLPFC) of same subjects in ROSMAP. Only the most significant H3K9ac peaks located within 50kb to 5hmC are listed.

Title: Supplementary Data 27

Description: Spearman correlation between PHFtau-associated 5hmC regions and H3K9ac ($\pm$ 50kb) in the brain cortex (DLPFC) of same subjects in ROSMAP. Only the most significant H3K9ac peaks located within 50kb to 5hmC are listed.

Title: Supplementary Data 28

Description: Spearman correlation between AD pathology-associated 5hmC and brain protein expression of same participants

Title: Supplementary Data 29

Description: Enrichment analysis for AD-associated 5hmC genes that are also correlated with protein expression in the same brain cortex of same participants

Title: Supplementary Data 30

Description: Enrichment analysis of AD diagnosis-associated 5hmC regions by GARFIELD

Title: Supplementary Data 31

Description: Enrichment analysis of A β -associated 5hmC regions by GARFIELD

Title: Supplementary Data 32

Description: Enrichment analysis of PHFtau-associated 5hmC regions by GARFIELD

Title: Supplementary Data 33

Description: Results of colocalization analysis

Title: Supplementary Data 34

Description: Sensitivity analysis showing that the association of 5hmC with A β load remained largely unchanged after controlling for PHFtau tangles

Title: Supplementary Data 35

Description: Sensitivity analysis showing that the association of 5hmC with PHFtau tangles remained largely unchanged after controlling for A β load