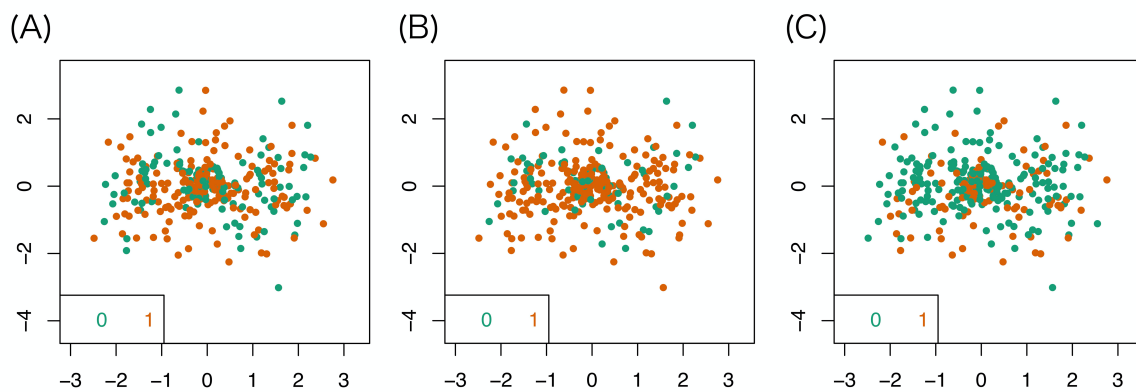


Supplementary Material

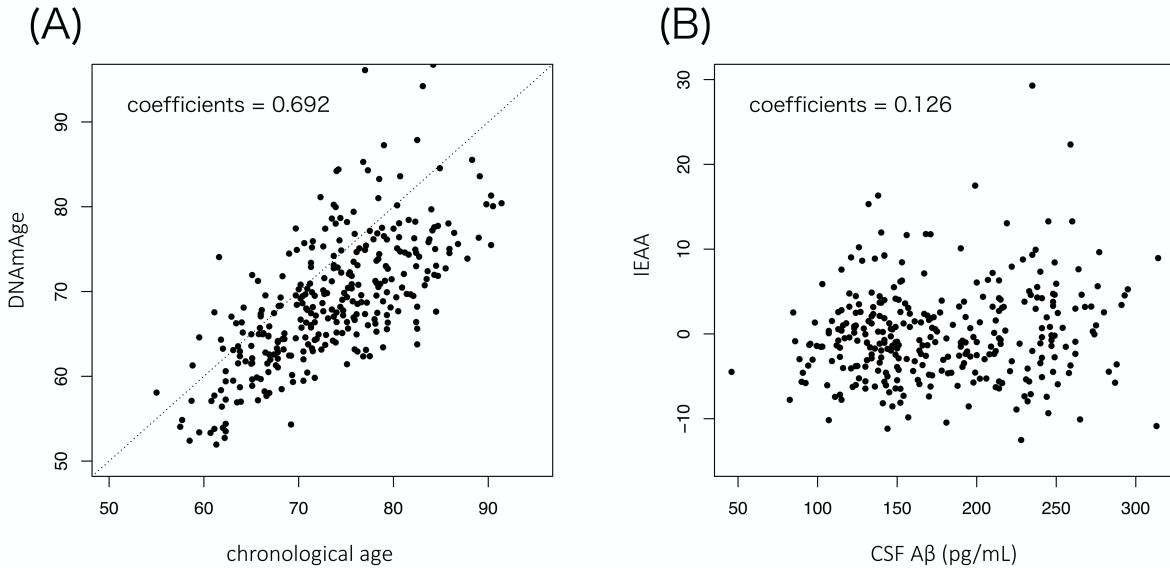
Attempt to Predict A/T/N-Based Alzheimer's Disease Cerebrospinal Fluid Biomarkers Using a Peripheral Blood DNA Methylation Clock

Supplementary Figure 1. MDS plot distribution between two groups according to the target of interest (e.g., A+ versus A-, or T+ versus T-).



MDS plot of top 1000 most variable CpG sites revealed no apparent separation in their distribution between the two subgroups regarding the target of interest, A+/- in (A), T+/- in (B), and N+/- in (C). Label “0” corresponds to negative (e.g., A-) and “1” corresponds to positive (e.g., A+).

Supplementary Figure 2. Correlation between the chronological age and the estimated epigenetic age, and correlation between the degree of aging acceleration and the CSF A β value.



The obtained methylation clock shows a clear correlation with the actual chronological age (A, coefficients = 0.692, $p < 0.001$). After adjustment for sex, *APOE* genotype, ethnicity, smoking history, CSF A β , t-tau, and p-tau, there is a weak but significant correlation between the IEAA and CSF A β (pg/mL) (coefficients = 0.016 ($p = 0.035$) in linear regression) (B, coefficients = 0.126 ($p = 0.025$) in Pearson's correlation) and between the EEAA and CSF A β value (coefficients = 0.017 ($p = 0.017$) in linear regression) (data not shown, coefficients = 0.116 ($p = 0.041$) in Pearson's correlation). However, there is no significant correlation between the IEAA/EEAA and CSF p-tau or t-tau values (data not shown). DNAmAge, methylation clock; IEAA, intrinsic epigenetic aging acceleration; EEAA, extrinsic epigenetic aging acceleration; CSF, cerebrospinal fluid.

Supplementary Table 1. Basic demographics of the included participants categorized according to the A/T/N system

A/T/N	n	actual age	sex	<i>APOE</i> ε4 allele(s) [0:1:2]	ethnicity (white/ others)	education	smoking (yes/no)	baseline diagnosis (AD/MCI/CN/uncertain)	MMSE	ADAS-cog13
A-T-N-	43	70 (65.75 ~ 76.5)	21:22	41:2:0	42:1	16 (14 ~ 18)	15:28	3:25:15:0	29 (28 ~ 30)	10 (8 ~ 13)
A+T-N-	26	74.4 (70.5 ~ 79.9)	18:8	17: 8:1	25:1	17 (15 ~ 19.75)	10:16	0:18:8:0	29 (28 ~ 29.75)	9 (6 ~ 15)
A+T+N-	77	72.7 (67.7 ~ 78.4)	37:40	33:36:8	72:4	16 (14 ~ 18)	38:39	5:52:20:0	29 (27 ~ 29)	13 (9 ~ 16)
A+T-N+	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
A+T+N+	91	75.6 (71.35 ~ 79.4)	45:46	29:46:16	89:2	16 (14 ~ 18)	37:54	32:45:13:1	26 (24 ~ 28)	23 (14.5 ~ 30.5)
A-T+N-	67	71.7 (67.8 ~ 76.9)	41:26	58:9:0	66:0	18 (14 ~ 19)	29:38	2:32:31:2	29 (28 ~ 30)	9 (7 ~ 12.5)
A-T-N+	1	71.3 (71.3 ~ 71.3)	1:0	1:0:0	1:0	16 (16 ~ 16)	0:1	0:1:0:0	29 (29 ~ 29)	11 (11 ~ 11)
A-T+N+	12	69.5 (65.9 ~ 77.7)	5:7	9:3:0	12:0	18 (16 ~ 19)	4:8	1:6:5:0	29 (28 ~ 29.25)	9.5 (7.75 ~ 12.5)

AD, Alzheimer's disease; MCI, mild cognitive impairment; CN, cognitive normal; MMSE, Mini-Mental Scale Examination; ADAS, Alzheimer's Disease Assessment Scale