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10-year epigenetic change: Age-associated CpGs are differentially heritable

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Epigenetic processes may contribute to differential health and mortality outcomes, however the etiologies of stability and change in DNA methylation have rarely been examined longitudinally. We evaluated 10-year change in DNA methylation in: (1) the Swedish Adoption Twin Study of Aging (53 pairs, 53% female; MAGE wave 1: 62.9 years, MAGE wave 2: 72.5 years); and (2) the Longitudinal Study of Aging Danish Twins (43 pairs, 72% female; MAGE wave 1: 76.2 years, MAGE wave 2: 86.1 years). A series of bivariate Cholesky models were fitted to M-values of 359,399 methylation probes from whole blood leukocyte DNA, adjusting for age, sex and scalar differences across country. Broad heritable contributions were on average small (23.8% wave 1) and decreased across 10 years (18.0% wave 2). Genetics contributed to 10-year stability while non-shared environment contributed to novel influences. Among CpG sites identified in epigenetic clocks and aging EWAS, stronger heritable influences were apparent, with up to 1.5- to 2.5-fold higher heritabilities. Among 776 available CpG sites from three epigenetic- clocks, ADE fit best for 490 CpGs and broad heritability estimates were 1.25- and 1.08-fold greater than the full CpG set or those where ADE fit best (p \ 0.00818), respectively. Hannum clock sites tended to show stronger genetic and shared environmental contributions than Horvath or Levine clock sites when ACE was the better fitting model (p \ 0.007), but not for ADE. Altogether, CPG sites related to aging may show relatively elevated heritable influences consistent with genetic regulation of the rate of biological aging.