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Development of Epigenetic Drift Scores to Study the Impact of HIV and Substance Use on Biological Aging

Epigenetic clocks have demonstrated remarkably high correlations with chronological age, but their reliability in predicting biological aging in people with HIV who use drugs remains inconsistent. Traditional clocks assume a linear relationship between epigenetic age and chronological age, focusing on deterministic mean-methylation shifts. Conversely, epigenetic drift age measures methylation variations over time, capturing more dynamic and heterogeneous changes of biological age. Epigenetic drift of CpG can be positive (i.e., increased variability in DNA methylation with age) or negative (i.e., decreased variability in DNA methylation with age). Using our established Epigenetic Drift Score (EDS) framework, our goal was to evaluate the impact of HIV infection and drug use on EDS in the Veteran Aging Cohort Study Biomarker Cohort (VACS-BC, N=1,507). We developed a positive drift score (EDS-pos) and a negative drift score (EDS-neg). We replicated 104 out of 204 CpG DNA dinucleotide (CpGs) in the EDS-pos and 39 out of 81 CpGs in the EDS-neg that were identified from our previous study. Using linear regression models, we confirmed that EDS-pos was positively associated with chronological age ($\beta=1.1 \times 10^{-3}$ $p=3.9 \times 10^{-3}$), while EDS-neg was negatively associated with chronological age in the VACS ($\beta=-8.4 \times 10^{-3}$ $p=7.1 \times 10^{-4}$). No significant association was found between EDS and sex, likely due to small number of women in the cohort. Genes near EDS-pos CpGs were enriched in neural system pathways, while those near EDS-neg CpGs were enriched in immune pathways. Next steps include examining the relationship between EDS and HIV/drug use in the VACS and replicating the findings in an independent cohort, MACS/WIHS Combined Cohort Study. Ultimately, we will develop a global epigenetic age score by integrating epigenetic clock and drift age measures to assess how both chronic HIV infection and drug use may accelerate biological age.

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