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Multi-Omic Biomarkers Are Associated with Cognitive Change in People with HIV

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Background: People with HIV (PWH) are at increased risk for age-related cognitive decline, however biomarkers that predict longitudinal cognitive change are lacking. We previously demonstrated cross-sectional associations between plasma cell-free mitochondrial DNA (cfmtDNA) and global cognition (MoCA). Herein, we extend our analysis to include plasma proteomics, epigenetic aging, and serial cognitive battery assessments to generate a multi-omics risk score to predict cognitive decline.

Methods: We analyzed data from 51 participants (median age 60, IQR:56-64) who completed a series of three study visits spanning a median of 6.8 years (range 5.4-8.4) and had complete data including baseline cfmtDNA, O-Link proteomic panel of 3,072 proteins, epigenetic age, and MoCA. Two serial follow-up visits, spaced a median of 2 years apart (range 1.7-3.3), entailed cognitive battery testing consisting of traditional neuropsychological tests and iPad-based assessments. Principal Components Analysis was used to derive five domain-specific scores representing verbal fluency, psychomotor speed, verbal learning and memory, visual search, and working memory. The Reliable Change Index (RCI) was calculated for each domain accounting for practice effect and standard deviation of results. Targeted proteomic composite sub-scores grouped z-scored proteins by biological pathway (IL-17 axis, myeloid activation, coagulation, IL-cytokine clusters), with FDR correction applied across all proteomic tests. We derived a seven-component multi-omics risk score by averaging standardized sub-scores across three biological domains: epigenetic aging, innate immune activation, and humoral/coagulation, with higher scores reflecting greater risk of cognitive decline. Bivariate

comparisons were evaluated by Pearson correlations, and multi-variate linear regression models were adjusted for baseline cognitive performance, age, AUDIT-C alcohol score, follow-up interval, and Social Vulnerability Index (SVI).

Results: A seven-component multi-omics risk score integrating epigenetic aging (PCPhenoAge residual, DunedinPACE), immune proteomics (IL-17 axis, myeloid), humoral/coagulation (coagulation, IL-cytokine sub-scores, inverted), and cfmtDNA trajectory predicted mean RCI ($\beta=-0.150$, $r=-0.422$, $p=0.004$). Participants with higher risk scores demonstrated cognitive decline. The IL-17 axis and myeloid activation subscores, and SVI, were strong predictors of working memory RCI ($\beta=-0.727$, $r=-0.577$, $p<0.0001$, FDR $q<0.0001$), ($\beta=-0.171$, $p=0.009$), respectively. Epigenetic age acceleration measured at the baseline visit (PCPhenoAge) predicted worse working memory RCI ($r=-0.385$, $p=0.005$) and processing speed RCI ($r=-0.314$, $p=0.034$) by Pearson correlation. Longitudinally, rising plasma cfmtDNA between visits two and three predicted working memory decline ($\beta=-0.536$, $r=-0.298$, $p=0.017$), with no associations observed for other cognitive domains. SVI independently predicted working memory performance ($\beta=-0.171$, $p=0.009$) and added incremental value beyond the biomarker risk score.

Conclusions: We generated a 7- component multi-omics risk score which included plasma cfmtDNA, epigenetic age, and proteomic signatures to predict reliable cognitive change across multiple domains in older PWH spanning upto 8 years of follow-up. The cfmtDNA signal was domain-specific to predict working memory decline. SVI emerged as an independent predictor of working memory, highlighting the contribution of socioeconomic factors alongside biological aging. Our composite multi-omics risk score predicting mean RCI shows promise for identifying at-risk individuals before clinical decline becomes apparent. Further research in a larger validation cohort is needed, as predictors were selected and validated in the same sample.

