Age-Related Alterations in DNA Methylation are Associated with AD Neuropathology

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INTRODUCTION

Age is the single largest risk factor for Alzheimer's Disease (AD). After age 65 the risk of AD doubles every five years, and by age 85, the prevalence is ~31%. Yet progression of AD etiology is hypothesized to begin decades earlier.

There is a growing emphasis to identify molecular changes that underlie the age-related increase in AD patjogenesis.

Aim: Use computational Approaches to identify epigenetic aging signatures in brain that relate to AD neuropathology.

MATERIALS & METHODS

Datasets

GSE74193: DLPFC DNA methylation (DNAm) data n=399 ages 20-97

ROSMAP: DLPFC DNAm data n=718 ages 65-108

Statistical Analysis

DNAm Data was available for just over ~450,000 CpGs

PCA was used as a data reduction tool

Elastic Net (Penalized Regression) was used to train a DNAm age predictor in DLPFC

The predictor was evaluated against AD clinical and pathological diagnostic variables

RESULTS

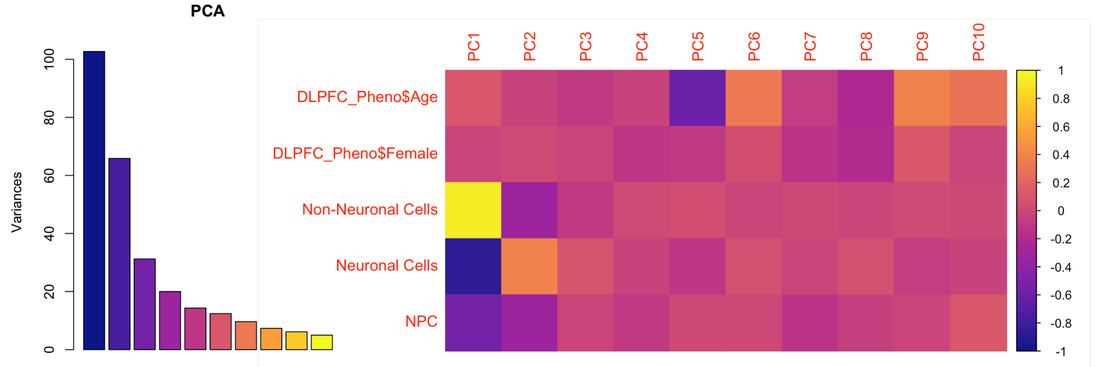

Figure 1: Screeplot of PCA run on ~450,000 CpG variables in DLPFC

Figure 2: Associations between DNAm PCs in DLPFC and phenotypic variables, including predicted cell proportions, age, and sex

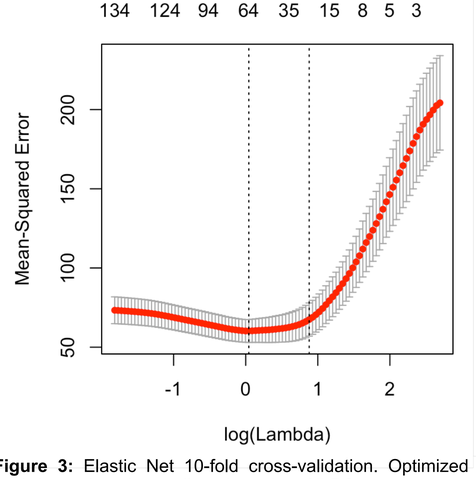

Figure 3: Elastic Net 10-fold cross-validation. Optimized lambda produced a predictor based on 65 PCs

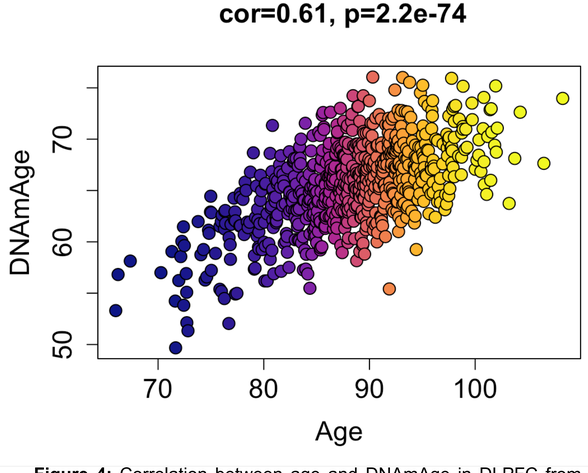

Figure 4: Correlation between age and DNAmAge in DLPFC from ROSMAP cohort

RESULTS CONT.

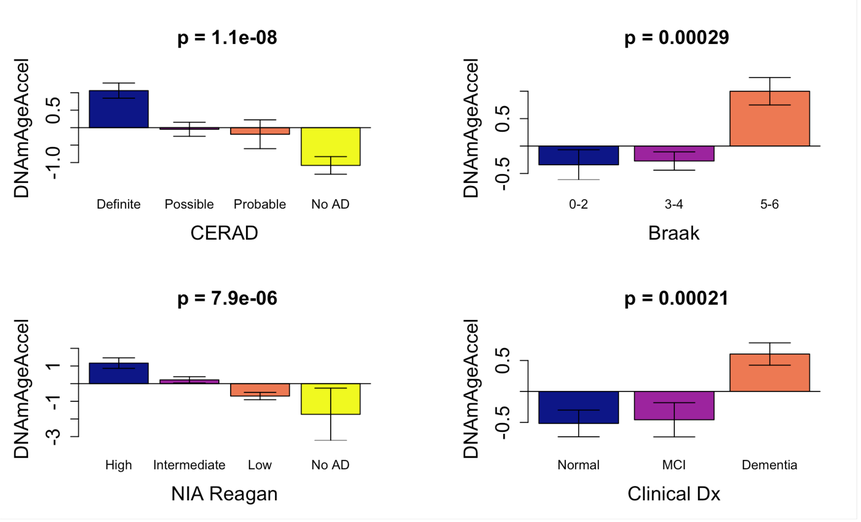

Figure 5: Associations between DNAmAge (adjusted for age, sex, study) and neuropathological and clinical diagnosis of AD.

CONCLUSION

Age-associated alterations in DNAm that are even apparent early in the life course, relate to AD neuropathology and cognitive functioning/dementia. There is evidence that these changes do not simply reflect changes in cell proportions, but may signal something about cellular aging or responses to aging. In moving forward it will be important to uncover mechanisms linking DNAm and AD and determine whether non-invasive biomarkers can be developed from these findings.

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