Biological Age Acceleration and Stochastic Epigenetic Mutations as Potential Biomarkers of Alzheimer's Disease Progression

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Statement

To the Dean of Faculty of Natural Sciences and Medicine LEPL Ilia State University

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As the author of the submitted thesis, I declare that the thesis is my original work and does not contain materials previously published, accepted, or defended by other authors, which are not mentioned or cited according to the citation rules.

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by an impairment of mental, psychological, and behavioral changes, and represents the most common cause of dementia worldwide. Despite extensive research, its underlying mechanisms remain unclear, and effective biomarkers for early diagnosis and monitoring of the disease's progression are limited. There is growing evidence that epigenetic dysregulation underlies the pathophysiology of Alzheimer's disease (AD). Differences in DNA methylation patterns, particularly stochastic epigenetic mutations (SEMs), have been proposed as potential markers for biological aging and molecular instability associated with disease.

In this study, the association between SEMs, DNA methylation age acceleration, and Alzheimer's disease progression was examined in 649 subjects recruited from the Alzheimer's Disease Neuroimaging Initiative (ADNI). The SEMs were quantified using both automatic detection and an interquartile range (IQR)-based threshold strategy. Additionally, several epigenetic clocks, including GrimAge, were utilized to assess biological age. The findings demonstrated a greater burden of SEM in AD patients in comparison to cognitively normal (CN) subjects. While GrimAge is strongly associated with chronological age, it had a limited ability to differentiate the age acceleration among the diagnostic groups. Additionally, the burden of SEM was weakly correlated, yet in a statistically significant way, with age acceleration.

Moreover, gene-level enrichment analysis has been conducted for sites with extreme SEM scores (± 4), representing outliers of hypo-/hypermethylation. According to the gene-level enrichment analysis, specific loci appeared to be affected across disease stages. It was notable that several genes previously linked to AD, including PPP2R2B, CYLD, NLRP1, ELMOD1, and NR1I2/NR1I3, demonstrated epimutational burdens specific to each disease stage. These findings suggest that extreme deviations in methylation of genes relevant to AD may appear and serve as potential biomarkers for disease progression.

Keywords: Alzheimer's disease; DNA methylation; stochastic epigenetic mutations; epigenetic clocks; biological age acceleration.

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