

Genome-wide DNA Methylation And Epigenetic Age Acceleration By Symptom Burden In Adults Aged <60 Years With Subjective Cognitive Decline

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- No difference in epigenetic age acceleration (HSB vs. LSB)
- PCDH19 hypermethylated in HSB
- Symptom burden linked to gene-specific changes, not biological aging
- PCDH19 methylation may flag symptom-related cognitive vulnerability

INTRODUCTION & METHODS	RESULTS	CONCLUSIONS	ACKNOWLEDGEMENTS
In adults <60 with subjective cognitive decline (SCD), co-occurring symptoms (anxiety, depression, fatigue, sleep disturbance, pain) may signal early neurodegeneration, and identifying their epigenetic correlates may reveal biological pathways underlying symptom-related cognitive vulnerability. SCD adults <60 were grouped as high (HSB, n=18) vs. low (LSB, n=31) symptom burden. Saliva DNA was assayed via Illumina MethylationEPIC; age acceleration (AA) was assessed by HorvathAA and GrimAA, and genome-wide CpG methylation compared between groups.	Figure 1. Epigenetic age acceleration by symptom burden group. HorvathAA and GrimAA (mean ± SD, in years) did not differ significantly between the high symptom burden (HSB, n=18) and low symptom burden (LSB, n=31) groups. HorvathAA: -1.65 ± 3.75 (HSB) vs. -0.21 ± 4.02 (LSB); GrimAA: 0.40 ± 4.75 (HSB) vs. -0.10 ± 4.30 (LSB). Error bars represent standard deviation; overlapping ranges indicate no significant group difference (n.s.). Figure 2. Differential methylation of PCDH19 in high symptom burden. Genome-wide CpG methylation analysis identified hypermethylation of PCDH19 in the HSB group. PCDH19 encodes a neuronal cell-adhesion molecule involved in neurodevelopment and synaptic organization, and has been implicated in cognitive and neuropsychiatric phenotypes—suggesting potential biological relevance to symptom-related cognitive vulnerability.	Among adults aged <60years with SCD, high multidimensional symptom burden was associated with <i>PCDH19</i> hypermethylation, whereas global epigenetic aging indices (HorvathAA and GrimAA) were not significantly different. These finding Suggest that symptom burden in younger adults with SCD may be better reflected by gene-specific epigenetic alterations than by accelerated epigenetic aging. Future studies with larger samples and longitudinal follow-up should validate the <i>PCDH19</i> methylation signals and evaluate its potential as a biomarker for symptom-related cognitive vulnerability.	This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (Ministry of Science and ICT) (No. 2022R1C1C1004826). CONTACT ALZHEIMER'S ASSOCIATION AAIC>26