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Letters to Editor

# Epigenetic markers as predictors of neurodegeneration in long COVID survivors

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## To the Editor

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The persistence of neurological symptoms in long COVID survivors including cognitive impairment, brain fog, and fatigue raises concerns about accelerated neurodegenerative processes. Recent developments suggest that epigenetic alterations, especially changes in DNA methylation and "epigenetic clock" acceleration, could serve as early predictors of future neurodegeneration [1]. Several longitudinal studies demonstrate that SARS-CoV-2 infection induces persistent epigenetic dysregulation. A 3-year cohort study using multiple epigenetic clocks showed that COVID-19 infection significantly accelerates biological aging measured by DNAmGrimAge, DNAmGrimAge2, and DNAmFitAge ($p < 0.05$) after adjustment for confounders [1]. Genome-wide methylation analysis six months post-infection revealed enhanced epigenetic drift, accelerated aging signatures, and disruption in pathways linked to metabolic, immune, and vascular health [2].

Specifically in long COVID and post-acute COVID-19 symptoms (PACS) subgroups, systematic reviews found preliminary evidence that DNA methylation profiles related to immune regulation, autonomic nervous system function, and metabolic genes differ from recovered individuals [3]. In mild/asymptomatic cases seven months post-infection, a household study identified reproducible differential methylation at CpG sites annotated to AFAP1L2 and PC genes implicated in cytoskeletal response and metabolic regulation suggesting a long-term molecular footprint of infection [4].

Parallel findings in neurodegenerative disease research affirm the relevance of epigenetic markers. DNA methylation dysregulation is consistently linked to neurological disorders and neurodegenerative diseases. In Alzheimer's disease (AD), DNA hypomethylation in promoter regions of genes like amyloid-β protein precursor (APP) and β-site APP-cleaving enzyme1 (BACE1) leads to their upregulation and the accumulation of Aβ.

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The APP gene has been noted as a potential diagnostic biomarker because it was consistently hypermethylated in the blood and brain of AD patients. For Parkinson's disease, hypomethylation in the alpha-synuclein (SNCA) intronl region is linked to an increase in gene expression. The provided document also notes that Ankyrin-1 (ANK-1) is associated with Alzheimer's and depression. Lastly, methylation at a gene's promoter is generally negatively associated with gene expression [5].

Emerging research also connects epigenetic age acceleration with cognitive decline and brain atrophy in aging populations. While not yet specific to long COVID, the use of multimodal epigenetic clocks correlates with neuroimaging-derived accelerated brain aging and predictive cognitive trajectories [6].

Taken together, these findings suggest plausible mechanistic overlap: persistent methylation alterations after COVID-19 could mirror patterns seen in neurodegeneration, and accelerated epigenetic aging may serve as a harbinger of future cognitive decline. Incorporating epigenetic profiling especially longitudinal tracking of epigenetic age and relevant CpG loci into long COVID follow-up could identify high-risk individuals before clinical neurodegeneration manifests. We therefore propose that: (i) longitudinal studies are urgently required to validate epigenetic signatures as prognostic biomarkers in long COVID survivors; (ii) combining epigenetic age acceleration measures with neuroimaging or fluid biomarkers may enhance risk stratification; (iii) future research should explore whether epigenetic-targeted interventions (e.g. diet, methyl donors, epidrugs) can mitigate neurodegenerative risk.

Given the prevalence of long COVID and the societal burden of dementia, early identification of at-risk individuals via epigenetic markers offers a timely, minimally invasive path for preventive strategy. We encourage clinical and translational researchers to prioritize this integrative approach.

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## Authors' contributions

Conceived the idea, designed the outline, and critical revision of this review article: SM. Conducted the literature search, interpretation of the literature, and drafted the initial manuscript: AA, SAH. All authors read and approved the final version of the manuscript.

## Conflict of interest

No potential conflict of interest was reported by the authors.

## Ethical declarations

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## References

1. Farkas G, Mahdaouy ZE, Babszky G, Jokai M, Torma F, Gu Y, et al. Associations of epigenetic aging and COVID-19: A 3-year longitudinal study. Geroscience. 2025;47(3):4889-4898. DOI: 10.1007/s11357-025-01635-4 PMID: 40210827
2. Calzari L, Dragani DF, Zanotti L, Inglese E, Danesi R, Cavagnola R, et al. Correction: Epigenetic patterns, accelerated biological aging, and enhanced epigenetic drift detected 6 months following COVID-19 infection: insights from a genome-wide DNA methylation study. Clin Epigenetics. 2024;16(1):158. DOI: 10.1186/s13148-024-01764-1 PMID: 39543717
3. Shekhar Patil M, Richter E, Fanning L, Hendrix J, Wyns A, Barrero Santiago L, et al. Epigenetic changes in patients with post-acute COVID-19 symptoms (PACS) and long-COVID: A systematic review. Expert Rev Mol Med. 2024;26:e29. DOI: 10.1017/erm.2024.32 PMID: 39435694
4. Hong P, Waldenberger M, Pritsch M, Gilberg L, Brand I, Bruger J, et al. Differential DNA methylation 7 months after SARS-CoV-2 infection. Clin Epigenetics. 2025;17(1):60. DOI: 10.1186/s13148-025-01866-4 PMID: 40251596
5. Rasmi Y, Shokati A, Hassan A, Aziz SG, Bastani S, Jalali L, et al. The role of DNA methylation in progression of neurological disorders and neurodegenerative diseases as well as the prospect of using DNA methylation inhibitors as therapeutic agents for such disorders. IBRO Neurosci Rep. 2022;14:28-37. DOI: 10.1016/j.ibneur.2022.12.002 PMID: 36590248
6. Humaira Amanullah F, Alam T, El Hajj N, Bejaoui Y. The impact of COVID-19 on "biological aging". Front Immunol. 2024;15:1399676. DOI: 10.3389/fimmu.2024.1399676 PMID: 38919619