Alzheimer’s disease-associated (hydroxy)methylomic changes in the brain and blood

abstract

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Abstract

Background
Considerable evidence suggests that epigenetic processes including DNA methylation and hydroxymethylation represent critical factors in the development and course of Alzheimer’s disease (AD).

Methods
Within the EPI-AD project (http://www.epi-ad.eu/), we performed an epigenome-wide association study (EWAS), assessing both DNA methylation and hydroxymethylation, using bulk tissues from the dorsal raphe nuclei (DRN), locus coeruleus (LC) and middle temporal gyrus (MTG) derived from AD patients and matched non-demented controls. We followed up these analyses by exploring methylomic signatures in microdissected serotonergic DRN cells using limiting dilution bisulfite pyrosequencing. In an independent (longitudinal) cohort, we compared the blood methylome of converters to AD dementia and non-converters at a preclinical stage.

Result
Within the DRN and LC, we revealed overlapping Braak stage-associated epigenetic abnormalities in TNXB, ANKRD2 and MBP. Interestingly, when comparing methylation levels of TNXB in individually isolated serotonergic neurons with those of non-serotonergic cells in the DRN, we found a significant interaction between cell-type and condition. The AD-associated methylation profiles were opposite in the serotonergic neurons and non-serotonergic cells, the latter of which resembled the EWAS data. Within the MTG, we revealed epigenetic differences close to or overlapping with genes such as OXT, CHRNB1, RHBDF2 and C3 that were associated with Braak staging. By comparing the blood methylome of converters to AD dementia and non-converters at a preclinical stage, we found that DNA methylation in the exact same region of the OXT promoter as seen in the MTG was associated with subsequent conversion to AD.

Conclusion
Overall, data on the MTG confirmed previous findings, identifying loci such as RHBDF2 and C3 that have been associated with AD in various EWAS studies on cortical brain regions. Notably, our brainstem work highlighted several novel epigenetic signatures that we hypothesize to play a pivotal role in early AD development. Furthermore, we show that dysregulation in TNXB methylation in the DRN is both dependent on the disease phenotype and the cell type analyzed, which warrants the need for cell-type specific neuroepigenetic studies in AD. Finally, we demonstrate that the detection of OXT methylation at pre-dementia stages holds potential relevance as a novel biomarker and therapeutic target.