PMI-AD

Blood N-glycomics reveals individuals at risk for cognitive decline in Alzheimer's disease

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Aims, research questions and working hypothesis
N-glycosylation is an important posttranslational modification on proteins that significantly influences their trafficking and function. There is increasing evidence that key pathogenic proteins in Alzheimer's disease (AD) are N-glycosylated, and that aberrant N-glycosylation may be an early pathogenic trigger in AD. We have previously found altered levels of N-glycans in cerebrospinal fluid of AD patients compared to controls at an early stage of the disease. Thus, we hypothesized that the N-glycome may be altered also in blood in early AD, and could be a prognostic or diagnostic biomarker of early AD. Our research questions were:

i) Could the blood N-glycome be used to distinguish patients with AD from healthy controls?
ii) Which N-glycan structures are significantly altered in AD compared to healthy controls?

Means/methods implemented by the consortium
To quantify N-glycans in blood, we developed a state-of-the-art method based on porous graphite carbon liquid chromatography coupled to tandem mass spectrometry (PGC-LC-MS/MS). Using this method, we analyzed levels of 62 N-glycan structures in 40 individuals (20 AD, 20 control, mean age: 82.2 ± 6.0 years) from the Swedish National Study on Aging and Care in Nordanstig (SNAC-N). Furthermore, the results were validated using a separate cohort from Norway, the Dementia Disease Initiation (DDI) cohort. We selected 60 individuals (20 individuals each from the A-T-, A+T-, and A+T+ groups, mean age: 67.1 ± 7.3 years) from the DDI cohort. Finally, we also estimated the structures of the 62 N-glycan structures that were identified in this study using MS/MS.

What are the outcomes of the project?
In the Swedish SNAC-N cohort, clustering analyses identified a group of patients (32,4% of the cohort) with low levels of blood N-glycans. In this group, the levels of 35 glycans were significantly decreased compared to the rest of the cohort. Low blood N-glycosylation was associated with AD dementia and lower cognitive function.

In the Norwegian DDI cohort, similar clustering methods revealed a group with low levels of blood N-glycans (37.9% of the cohort). In this group, levels of 22 N-glycans were significantly decreased compared to the rest of the cohort. Low blood N-glycosylation was associated with *APOE4* genotype and future cognitive decline but, importantly, not with amyloid/tau status. In summary, low blood N-glycosylation was associated with poor cognitive prognosis in a younger cohort, and with clinical AD dementia in an older cohort. 14 N-glycan structures were significantly decreased in the low N-glycosylation group of both cohorts and could be further developed as AD biomarkers.

Significance and impact of the work on the field
In this study, we provided the most extensive characterization of the blood N-glycome to date in the context of AD. We show that low levels of N-glycans in blood were associated with poor cognitive prognosis in an amyloid/tau independent manner. Thus, blood N-glycome profiling could be developed as a minimally invasive prognostic biomarker in AD. Furthermore, our findings add to the evidence that altered N-glycosylation is present in early AD.

Next steps and future challenges
Our method could be used as a useful reference for the development of glycan biomarkers in AD, but also in other diseases where aberrant N-glycosylation is important, such as cancer or autoimmune diseases. To find more specific glycan biomarkers for AD, we will develop glycoproteomic methods to identify the specific proteins to which the abnormal N-glycans are attached. Finally, identification of specific proteins with abnormal N-glycosylation will open the path for targeted therapies against AD.