Blood protein markers predict 15-year risk of dementia

Using a data-driven proteomics strategy from a prospective community-based cohort with long-term follow-up, this study reports that plasma levels of glial fibrillary acidic protein (GFAP) can predict the risk of dementia, even 15 years before disease diagnosis. Our findings have important implications for early screening and interventions for dementia.

Publisher's note

The mission

Dementia — including Alzheimer's disease (the most common dementia form), vascular dementia and other dementia types — often progresses slowly over many years from the asymptomatic stage to a fully expressed clinical syndrome[1]. Amyloid-β and tau are well-established diagnostic hallmarks of Alzheimer's disease, but they have limited efficiency in predicting disease progression[2]. For other types of dementia, biomarker research is relatively scarce and, currently, no established fluid biomarkers exist for vascular dementia. Although certain blood markers have shown strong associations with the risk of dementia, high-performing markers for risk prediction and monitoring are still needed[3]. As no effective therapies are currently available and relevant clinical trials are fraught with hurdles, correctly determining whether a person will progress to dementia in the near future has become a public health priority[4]. The timely referral of populations who are at risk for early diagnosis and prompt intervention is expected to have a positive effect on disease outcomes[1,4]. However, early prediction of dementia remains a major challenge for clinicians. The advancement of blood-based proteomics might facilitate early screening for dementia risk in the general population.

The discovery

Using plasma proteomics data from 52,645 UK Biobank participants who did not have dementia at baseline and who we followed up longitudinally, we estimated the association of 1,463 baseline blood proteins with a later diagnosis of dementia under Cox proportional hazard regression models. The proteins that were significantly associated with dementia were fed into a light gradient boosting machine classifier, and each protein was ranked according to its contribution to predicting risk of dementia, followed by a sequential forward selection strategy to further filter out the few proteins that were most predictive of dementia incidence. Receiver operating characteristic analyses were then performed to evaluate the accuracy of the above-selected protein predictors of dementia. Kaplan–Meier survival curves and Cox hazard models were used to explore the clinical progression of dementia events over time. Lastly, temporal trajectories were depicted to observe the dynamic evolution of plasma proteins during the 15 years that preceded dementia diagnosis.

Of the total 1,463 plasma proteins tested in this study for their associations with dementia, GFAP, neurofilament light polypeptide (NEFL), and growth/differentiation factor 15 (GDF15)[5], which had all previously been associated with dementia, as well as the newly identified biomarker latent-transforming growth factor β-binding protein (LTBP2) consistently had the most significant associations with incident all-cause dementia, Alzheimer's disease and vascular dementia, and ranked high in terms of weight for dementia prediction.

When tested alone, each of these proteins demonstrated modest predictive accuracies. However, when combined with basic demographic data (age, sex, education and *APOE* ε4 status), the levels of GFAP or of GDF15 in the blood could reliably predict risk of all-cause dementia and Alzheimer's disease or vascular dementia. The combination of GFAP or GDF15 with demographic factors could reliably predict dementia incidence, even 10 years prior to diagnosis (Fig. 1a). Individuals with higher GFAP levels (normalized protein expression value > 0.381) were 2.32 times more likely to develop dementia. Notably, GFAP and LTBP2 were both highly specific for dementia prediction, but NEFL or GDF15 were not. Furthermore, we found that blood levels of GFAP and NEFL begin to increase 15 years before dementia diagnosis (Fig. 1b).

The implications

Our findings associate the levels of GFAP, NEFL, GDF15 and LTBP2 in the plasma with incident all-cause dementia, Alzheimer's disease and vascular dementia, and emphasize their applicability for dementia prediction. Of note, GFAP and LTBP2 could serve as promising predictive biomarkers specific to dementia. Combining GFAP with basic demographic indicators achieved a desirable prediction for dementia, even 15 years before the diagnosis. These findings have substantial implications for screening individuals at high risk for dementia and for early intervention.

This work stands as a large cohort study of blood proteomics and dementia, but was confined to a specific population from the UK Biobank without external validation. Consequently, the question remains whether our conclusions can be extrapolated to broader populations. Future research will concentrate on validating our findings across varied cohorts. Additionally, delving into the fundamental mechanisms that connect blood biomarkers and dementia represents a crucial avenue for future exploration.
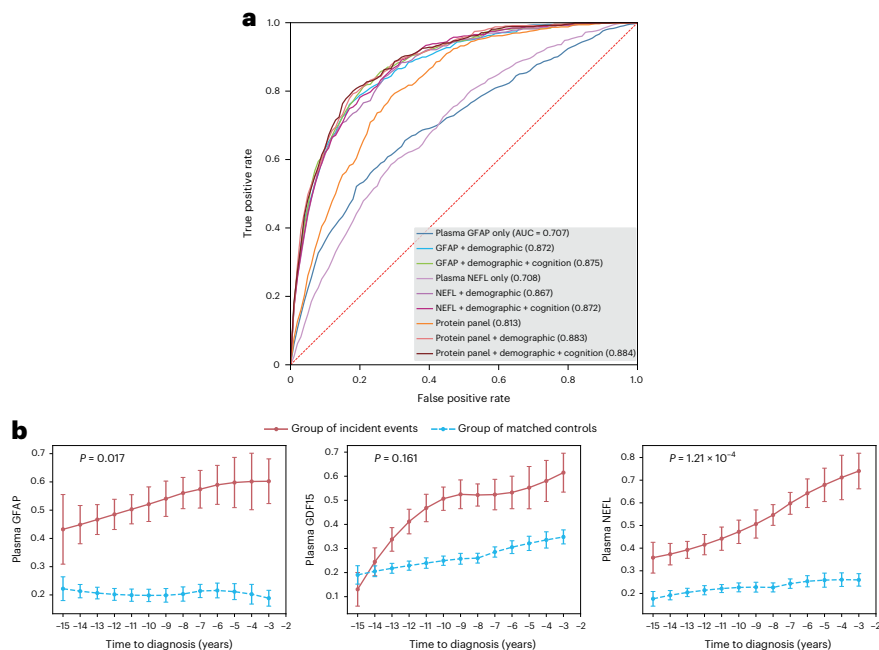
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FIGURE

Fig. 1 | Predictive performance and temporal trajectories of plasma proteins. a, Predictive accuracies of plasma proteins for risk of dementia, quantified as area under the curve (AUC) alone or in combination with other variables. Within the combined model, demographic indicators included age, sex, education, and *APOE* ε4 status, and cognitive tests included pairs matching time and reaction time. The protein panel combines the most predictive proteins, including GFAP, EDA2R, NEFL, GDF15, BCAN, NPTXR, LTBP2, HPGDS and CDON. **b.** The dynamic changes of plasma GFAP, GDF15 and NEFL before developing all-cause dementia, Alzheimer's disease and vascular dementia. Mann–Kendall trend tests were used to examine the slope differences of plasma protein levels over time for individuals with incident dementia (red curves) compared with those of control individuals (blue curves). © 2024, Guo, Y. et al.

BEHIND THE PAPER

Dementia has quickly emerged as one of the most costly, fatal and burdensome diseases of this era[1]. To rank blood markers on the basis of their predictive potential of dementia risk, we leveraged the high-throughput proteome assays, substantial sample size and long follow-up duration provided by the UK Biobank. Initially conceived to conclude at the stage of predictive accuracy, our study continued to delve deeper into the dynamic trajectories, sparked by our curiosity about the emerging consequential findings.

Interestingly, the dynamics of plasma proteins provided observable evidence of early signs of dementia beginning 15 years before the diagnosis, which has clear implications for future prognosis and monitoring. It was sheer enthusiasm that carried us to the end. **Y.G. & J.-T.Y.**

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