Emerging Dementia Biofluid Biomarker Candidates Identified in Human Proteomic Studies (2021-2025)

Authors: Anne-Li Lind[1], Emma Stam[1], Ryan Lamers[2], Mariana Fontes[1]
[1]Olink Proteomics AB, Uppsala, Sweden; [2]Olink Proteomics, Massachusetts, USA
Presenting author: anneli.lind@olink.com

Background

- Alzheimer's disease (AD) and other dementias are among the top causes of death globally.
- As the world population ages, the incidence of age-related neurodegenerative diseases is also increasing.
- Recently approved and new AD-modifying treatments promise more years of independence for patients and families affected by dementias. Such treatments highlight the need for biomarkers along the entire drug development and patient care journey.
- There is an unmet clinical need for biomarkers that enable the early detection of AD and other dementias.
- Recent proteomic analyses of biofluids have identified numerous emerging dementia biomarker candidates.

Aim

1. Identify trends in emerging dementia biomarkers.
2. Understand the significance and pathway context of emerging dementia biomarkers for future validation and potential clinical application for improved outcomes.

Methods

Review of 82 peer-reviewed dementia studies (published 2021-2025) using the Proximity Extension Assay (PEA™) in cerebrospinal fluid (CSF) and blood samples (including UK Biobank data).

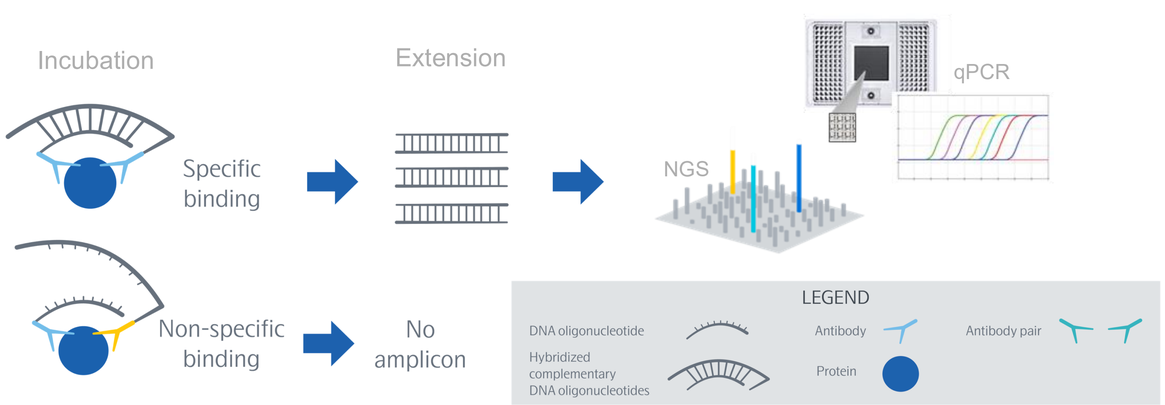

Figure 1. Proximity Extension Assay (PEA) with readout using either quantitative real-time PCR (qPCR) or Next Generation Sequencing (NGS) leverages dual antibody recognition with sample- and protein-specific barcoding for high sensitivity and specificity. The "Incubation" step involves incubating the proteomic samples with antibodies conjugated to DNA oligonucleotides. When the correct antibody pair binds its target protein, the oligonucleotides hybridize. The "extension" step involves extending and amplifying the hybridized oligonucleotide to create unique protein-specific DNA barcodes. The hybridization and extension are immediately followed by PCR amplification. The resulting DNA amplicon can then be quantified either by microfluidic qPCR on Olink® Signature Q100, or on an NGS platform, depending on the specific Olink product used.

Results

The 82 dementia studies focused on multiple biomarker types, spanning at least four FDA biomarker classes - risk, diagnostic, prognostic and pharmacodynamic.

The majority of studies analyzed plasma, followed by CSF.

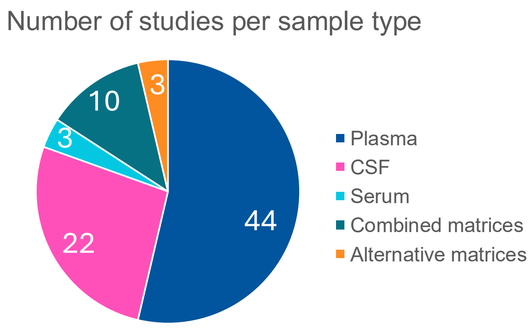

Figure 2. Of the 82 studies, 44 were plasma only, 22 were CSF only, 3 were serum only, 3 alternative matrices, and 10 studies combined multiple matrices.

Over 268 dementia biomarker candidates

Our analysis revealed that the 82 original dementia studies identified over 268 proteins regulated in human biofluids. Multiple studies confirmed the involvement of established biomarkers, such as GFAP (astrocytic activation) and NEFL (neurodegeneration).

- 19 proteins were identified in three studies or more (Figure 3).
- 44 proteins were identified in two studies.
- 205 proteins were identified in a single study.

Results, continued

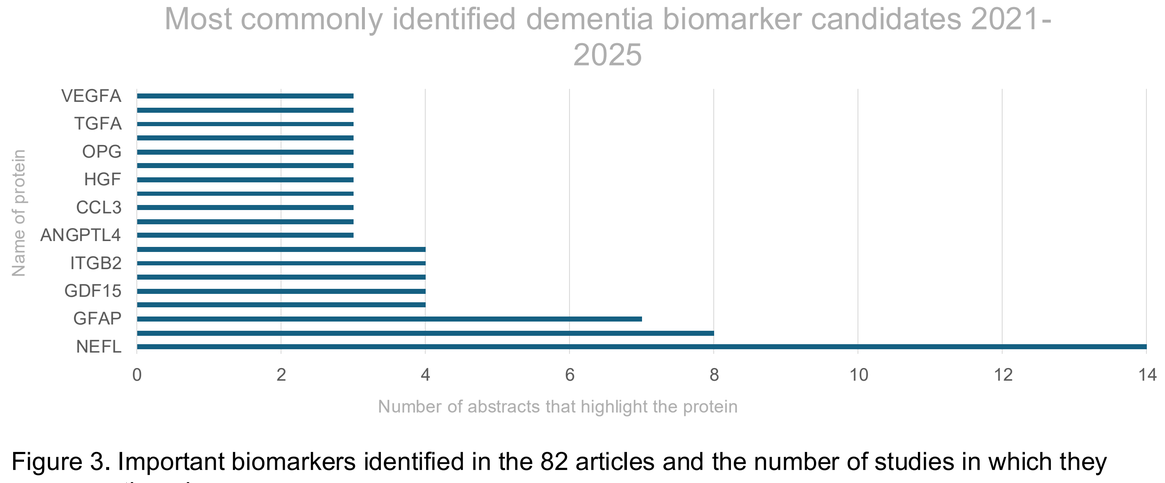

Figure 3. Important biomarkers identified in the 82 articles and the number of studies in which they were mentioned.

UK Biobank data based on PEA™

14 of the dementia publications used UK Biobank data to identify plasma proteins associated with dementia risk (all-cause dementia, AD and cerebrovascular dementia).

The 14 studies highlighted 39 dementia risk associated plasma proteins and 7 were identified in >1 UK Biobank analysis (Figure 4).

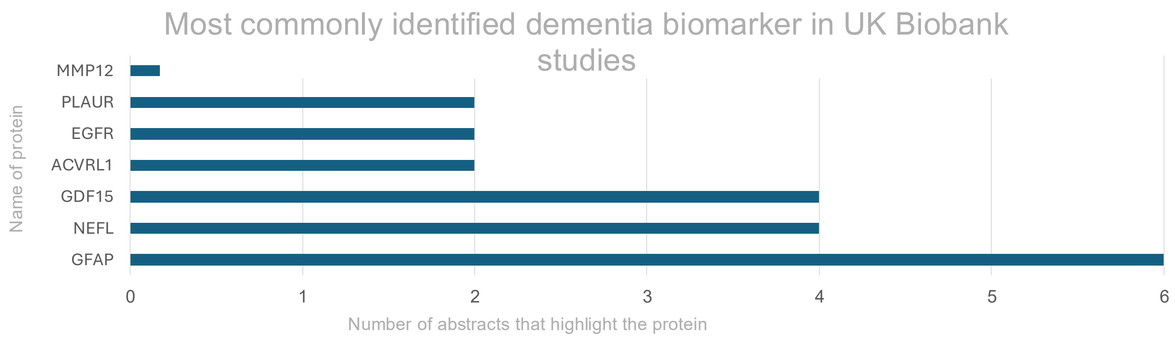

Figure 4. Important biomarkers identified in all 14 studies based on UK Biobank data. 7 proteins were identified in >1 UK Biobank analysis. GFAP was associated with dementia in 6 publications, GDF15 and NELF in 4; and ACVRL1, EEGFR, MMP12 and PLAUR were each identified in 2.

Using Olink® Insight, we highlight the key pathways in which emerging dementia biofluid biomarkers belong (based on UK Biobank PEA analysis in Figure 5).

Figure 5. Pathways of dementia risk based on 14 UKB dementia studies from 2021-2025.

Conclusions

- Recent biofluid proteomic studies have identified novel risk, diagnostic, prognostic, and pharmacodynamic biomarker candidates for cognitive decline, warranting further validation.
- Out of 268 identified dementia biomarker candidates, several established biomarkers were confirmed, and many were newly discovered.
- The biomarkers in the 14 studies based on UK Biobank data map onto biological pathways including signal translation, immune system, and metabolism.

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