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CSF Biomarkers

# Novel diagnostic cerebrospinal fluid biomarkers for pathologic subtypes of frontotemporal dementia identified by proteomics

Charlotte E. Teunissen[a,*], Naura Elias[a], Marleen J. A. Koel-Simmelink[a], Sisi Durieux-Lu[a], Arjan Malekzadeh[a], Thang V. Pham[b], Sander R. Piersma[b], Tommaso Beccari[c], Lieke H. H. Meeter[d], Elise G. P. Dopper[d,e], John C. van Swieten[d,e], Connie R. Jimenez[b,*], Yolande A. L. Pijnenburg[e,*]

[a]*Neurochemistry Laboratory and Biobank, Department of Clinical Chemistry, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands*

[b]*OncoProteomics Laboratory, Department of Medical Oncology, VU University Medical Center, Amsterdam, The Netherlands*

[c]*Department of Pharmaceutical Sciences, University of Perugia, Perugia, Italy*

[d]*Department of Neurology, Erasmus Medical Center, Rotterdam, The Netherlands*

[e]*Alzheimer Center & Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands*

**Abstract**

**Introduction:** Reliable cerebrospinal fluid (CSF) biomarkers enabling identification of frontotemporal dementia (FTD) and its pathologic subtypes are lacking.

**Methods:** Unbiased high-resolution mass spectrometry–based proteomics was applied on CSF of FTD patients with TAR DNA-binding protein 43 (TDP-43, FTD-TDP, n = 12) or tau pathology (FTD-tau, n = 8), and individuals with subjective memory complaints (SMC, n = 10). Validation was performed by applying enzyme-linked immunosorbent assay (ELISA) or enzymatic assays, when available, in a larger cohort (FTLD-TDP, n = 21, FTLD-tau, n = 10, SMC, n = 23) and in Alzheimer's disease (n = 20), dementia with Lewy bodies (DLB, n = 20), and vascular dementia (VaD, n = 18).

**Results:** Of 1914 identified CSF proteins, 56 proteins were differentially regulated (fold change >1.2, $P < .05$) between the different patient groups: either between the two pathologic subtypes (10 proteins), or between at least one of these FTD subtypes and SMC (47 proteins). We confirmed the differential expression of YKL-40 by ELISA in a partly independent cohort. Furthermore, enzyme activity of catalase was decreased in FTD subtypes compared with SMC. Further validation in a larger cohort showed that the level of YKL-40 was twofold increased in both FTD pathologic subtypes compared with SMC and that the levels in FTLD-tau were higher compared to Alzheimer's dementia (AD), DLB, and VaD patients. Clinical validation furthermore showed that the catalase enzyme activity was decreased in the FTD subtypes compared to SMC, AD and DLB.

**Discussion:** We identified promising CSF biomarkers for both FTD differential diagnosis and pathologic subtyping. YKL-40 and catalase enzyme activity should be validated further in similar pathology defined patient cohorts for their use for FTD diagnosis or treatment development.

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*Keywords:* Biomarkers; Cerebrospinal fluid; Proteomics; Frontotemporal dementia; Pathology; TDP-43; Tau; Differential diagnosis

## 1. Introduction

Frontotemporal dementia (FTD) is the second most prevalent dementia of patients aged <65 years that clinically presents with either behavior and personality changes or

*Shared senior authors.

*Corresponding author. Tel.: +31-20-4443680; Fax: +31-20-4443895.

E-mail address: c.teunissen@vumc.nl

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language disturbance. The disease is often misdiagnosed in the early stage, either as a psychiatric disorder or as a different type of dementia such as Alzheimer's dementia (AD). The pathology is characterized by two main distinct subtypes, i.e., tau pathology accounting for roughly one half of cases and TAR DNA-binding protein 43 (TDP-43)–pathology for the other half [1,2]. The clinical spectrum of FTD does not correlate with the distinct pathologies, except when the underlying pathology of FTD is predicted by the presence of an autosomal dominant mutation, which is found in only 20%–30% of the patients [3]. Mutations in the C9orf72 and GRN genes correspond to TDP-43 pathology, and mutations in the microtubule-associated protein tau (MAPT) to tau pathology, but an autosomal dominant family history is found in only 20%–30% of the patients. In addition, FTD with amyotrophic lateral sclerosis or motor neuron disease is almost always associated with underlying TDP-43 pathology [4]. Correct diagnosis and subtyping is very relevant to determine patient management plans and boost therapy development, especially to develop treatments targeting either tau or TDP-43 pathologic mechanisms.

Thus far, no reliable biomarker or set of biomarker with both high sensitivity and high specificity is available for FTD, let alone its pathologic subtypes. The cerebrospinal fluid (CSF) biomarkers for AD, i.e., (p)Tau and amyloid β-42 (Aβ42), appear to be of limited value for the diagnosis of clinical FTD [5,6], although a prognostic value of tau in diagnosed FTD patients has been reported [7]. A reduced CSF P-tau-181-to-tau ratio has recently been found to identify patients with TDP-43 pathology at a sensitivity and specificity of each 82% [8], which awaits independent validation.

A good technology to identify multiple novel biomarkers in body fluids is mass spectrometry–based proteomics [9]. So far, no comprehensive discovery at the protein level has been performed as previous proteomics studies used low resolution methods for profiling of a limited set of abundant CSF peptides or proteins in clinically defined FTD patient groups [10–14]. A recent immunoassay-based proteomics study focused on an analysis of 151 biomarkers for different pathologic subtypes of FTD. This has yielded several proteins that discriminated FTD-TDP-43 and FTD-tau, including interleukins (IL-23 and IL-7), which combined had an 86% sensitivity and 78% specificity [15].

In the present study, we aimed to identify novel pathology-specific biomarkers for FTD by in-depth protein profiling of antemortem collected CSF of FTD patients with known underlying pathology. We applied unbiased CSF proteomics methods [16] in patients with confirmed tau or TDP-43 pathology, either by genetic testing or postmortem analysis, and controls with subjective memory complaints (SMC). We validated the findings using alternative assays in a largely independent cohort and in patients with other dementias.

## 2. Methods

### 2.1. Patients

Patients with established FTD subtypes and SMC were included from the biobanks of the Amsterdam Dementia Cohort and from the Erasmus MC. The method to define the pathology to is outlined in Table 1, which shows that the majority was based on postmortem examination. FTD pathology was reviewed according to international criteria [17]. Pathologic examination was performed according to protocolized procedures by the Dutch brain bank, including specific immunostaining for TDP-43 pathology and tau pathology. Genetic testing was performed for mutations in the *MAPT* and progranulin genes and for the hexanucleotide repeat at *C9orf72*. The discovery cohort contained 30 patients, the validation cohort 53 patients, and 17 of the 53 patients in the validation cohort overlapped with the discovery cohort, as outlined in Table 1.

All subjects underwent extensive dementia screening at baseline, including physical and neurologic examination, mini-mental state examination (MMSE), neuropsychological investigation, electroencephalogram, magnetic resonance imaging, and laboratory tests, including lumbar puncture. Dementia diagnoses were made by consensus in a multidisciplinary meeting according to standard criteria [18,19]. Probable AD was diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders association [20], and all patients met the core clinical National Institute on Aging-Alzheimer's Association criteria [21]. Definite FTD was diagnosed using the criteria of Rascovsky et al. [2]. Control groups of subjects with SMC consisted of individuals who presented with cognitive complaints, but cognitive and laboratory investigations, were normal and criteria for mild cognitive impairment, dementia, or any other neurologic or psychiatric disorders known to cause cognitive complaints were not met. CSF biomarkers abeta (1–42), tTau, and pTau were not used for the clinical diagnosis of any of the patients. Groups were matched for age and gender. Patient characteristics of the discovery and validation cohorts are presented in Table 1.

The study was performed according to the ethical principles of the Declaration of Helsinki and was approved by the local ethics committee. We obtained written informed consent from all subjects participating in the study.

### 2.2. CSF biobanking and proteomics analysis

CSF and blood were collected and stored at −80°C in polypropylene tubes (Sarstedt, Nümbrecht, Germany) after centrifugation within 1 hour after withdrawal according to international biobanking consensus guidelines optimized for CSF proteomics [22]. CSF Aβ42, total tau, and p-tau were measured with commercially available enzyme-linked immunosorbent assays (ELISAs; INNOTEST Fujirebio, Ghent, Belgium) on a routine basis as described previously [23].

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