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Importance of fluid biomarkers in FTD

Frontotemporal dementia (FTD) is a clinically, genetic and pathologically heterogeneous disorder. Although promising CSF and blood biomarkers have been identified, including neurofilament light chain (NfL), there is an unmet need for FTD-specific biomarkers. Such biomarkers could help discriminate FTD from other dementias, in particular Alzheimer's disease, and non-neurodegenerative disorders with similar clinical presentations.

Genetic FTD cohorts, such as FTD-RisC and GENFI, have the unique potential to detect the earliest biomarker changes in the presymptomatic and prodromal stages of disease, which has been demonstrated for NfL and neuronal pentraxin 2 (NPTX2). In addition, since the underlying pathology is known based on the genetic mutation, genetic FTD cohorts may help us identify biomarkers that can accurately predict pathological subtypes in sporadic FTD patients. This is especially important in light of pathology-directed therapeutic strategies. Promising developments include detection of novel tau isoforms and real-time quacking induced conversion (RT-QuIC)assays for TDP-43.

FTD pathophysiology is highly complex and much remains to be elucidated. Biomarkers studies may provide further insights into the role and timing of various processes including neuroinflammation, synaptic and lysosomal dysfunction. Given these complexities, the combined use of multiple biomarkers may be more powerful than single biomarkers. Using multiple biomarkers simultaneously, prognostic models can be built to determine biomarker-based disease stages on the single subject level, which could enable selection and stratification of patients for clinical trials, as well as monitor disease progression.