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Peripheral monitoring of neurodegeneration in early-onset dementias using cell-free DNA

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State of the Art:
Neurodegeneration is central to a variety of human diseases, including frontotemporal dementias (FTD). Diagnosis of FTD relies on clinical and neuroimaging examination post-symptom onset, with limited biomarkers available for pre-symptomatic stages. Identification of pre-symptomatic biomarkers, particularly analysable by blood test, would provide earlier, more economical methods of diagnosis, and facilitate enrolment in therapeutic clinical trials. Cell-free DNA (cfDNA) derived from brain tissue holds great potential as a blood-based biomarker for detecting and monitoring neurodegeneration.

Methodology:
A longitudinal cohort of early-onset dementia cases, including FTD-related syndromes (n=76), with bloods and longitudinal imaging available was included in the study. Targeted Next-Generation Sequencing was used to quantify cfDNA from peripheral blood, with neuron- and glia-specific DNA methylation profiles used to determine cell-of-origin. Neuroimaging was analysed to determine patterns of atrophy and their relationship with brain-derived cfDNA levels. Sub-sequence-level machine learning was employed to identify potential novel cfDNA signatures that could differentiate cases.

Results:
Brain-derived cfDNA was detected in 94.5% of samples, with increased levels of neuron- and glia-cfDNA observed in cases versus controls. Comparison of brain-derived cfDNA and neuroimaging showed a strong correlation between high initial brain-derived cfDNA and syndrome-specific patterns of atrophy. Machine learning identified novel, differentially expressed cfDNA sequences in a subset of cases, indicating dementia-specific cfDNA signatures that could help inform development of diagnostic algorithms.

Conclusion:
Our work provides substantial confirmation of the potential of cfDNA as a diagnostic biomarker in FTD and lays the groundwork for future design and development of blood-based testing for neurodegeneration.

Conflicts of interest

N/A