Frontotemporal Dementia Diagnosis Using Circulating microRNA Biomarkers

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Overview

Frontotemporal dementia (FTD) is a heterogeneous neurodegenerative disorder characterized by frontal and temporal lobe atrophy, typically manifesting with behavioral or language impairment. Because of its heterogeneity and lack of available diagnostic laboratory tests, there can be a substantial delay in diagnosis. Cell-free, circulating, microRNAs (miRNAs) are increasingly investigated as biomarkers for neurodegeneration, but their value in FTD is not yet established. Here, we developed a novel method that enables earlier detection of FTD and accurate identification of patients for clinical trials using circulating, cell-free miRNAs as FTD biomarkers.

Background and Unmet Need

FTD is the second most common form of dementia, after Alzheimerâ€™s disease below the age of 65. Due to heterogeneity in clinical presentation, FTD can be difficult to diagnose1 (on average, accurate diagnosis takes 3.6 years). Previous studies have aimed to develop cell-free biomarkers for FTD, but none of these have shown use for diagnosis. There is an urgent unmet need for biomarkers for FTD in bodily fluids â€“ blood and cerebrospinal fluid (CSF), to facilitate clinical trial design and the enrollment of patients into clinical cohorts with reduced phenotypic variability. Furthermore, circulating biomarkers may provide pharmacodynamics approximation for the efficacy of experimental therapies in trials, thus reducing trial size, length and overall costs. Previous studies have assessed the initial potential of miRNAs, a class of endogenous small non-coding RNAs, as diagnostic FTD biomarkers including miRNA analysis in plasma2, CSF and serum, and CSF exosomes, but no definitive markers have so far been found.

The Solution

Prof. Eran Hornstein and his team developed a novel machine learning-enabled method that diagnoses, classifies, and predicts FTD based on plasma-circulating cell-free miRNA biomarkers3.

Technology Essence

The team profiled blood plasma miRNA from FTD patients, and using next-generation sequencing technology, discovered a signature composed of 20 miRNAs that could classify FTD. This signature that was found in an initial cohort was informative when applied to a validation cohort. These observations suggest that miRNAs can be potentially utilized in clinical sampling as diagnostic FTD markers, which is needed because of non-specific early symptoms and overlap with other degenerative and non-degenerative conditions. In addition, machine learning algorithms were implemented which resulted in an improved classification precision with a smaller panel of miRNA classifiers.

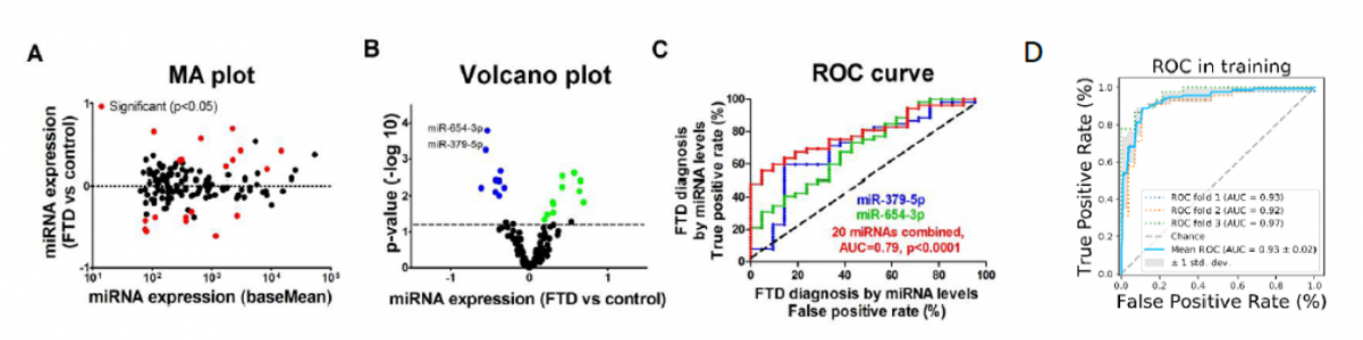

Figure 1: Predictive value of differential miRNA expression in FTD plasma: (A) MA plot of differential miRNA expression in FTD and healthy control; (B) A volcano plot of differentially expressed miRNAs between FTD and healthy control; (C) Receiver Operating Characteristic (ROC) curves demonstrating the prediction capacity superiority of the combinatorial signature of the 20 miRNAs over any individual miRNA. (D) ROC curves in the ML training set: true positive rate (y-axis) vs. false positive rate (x-axis). Mean values and variance when data from 293 samples with 3-fold cross validation.

Applications and Advantages

- Effective biomarkers for FTD diagnosis in the clinic
- miRNA pharmacodynamic biomarkers for monitoring drug effects
- Improves diseases subtyping
- Can be used to distinguish between ALS and FTD conditions
- Reduces diagnostic delay
- Cost-effective tool to facilitate clinical development of FTD drugs

Development Status

Prof. Hornstein and his team performed next-generation miRNA sequencing on cell-free plasma from 168 FTD cases and 125 controls. Based on cell-free plasma miRNA profiling by next-generation sequencing and machine learning approaches, they develop nonlinear prediction models that accurately distinguish FTD from non-degeneration controls in ~90% of cases.

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References

Magen, Iddo, Nancy-Sarah Yacovzada, Jason D. Warren, Carolin Heller, Imogen Swift, Yoana Bobeva, Andrea Malaspina, Jonathan D. Rohrer, Pietro Fratta, and Eran Hornstein. 2020. miRNA Biomarkers for Diagnosis of ALS and FTD, Developed by a Nonlinear Machine Learning Approach. medRxiv. DOI: 10.1101/2020.01.22.20018408 [1]

Patent Status

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