Cell-free microRNA as a Prognostic Biomarker for Amyotrophic Lateral Sclerosis (ALS)

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Overview

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder of the human motor neuron system, for which no effective treatment exists. Variability in the rate of disease progression limits the efficacy of ALS clinical trials, suggesting that developing better biomarkers for prognosis will facilitate therapeutic progress. We developed a novel method that predicts ALS disease course using the plasma level of miR-181. When coupled with the established protein biomarker neurofilament light chain (NfL), this prognostic tool boosts precision of patient stratification and may greatly enhance the power of ALS clinical trials.

Background and Unmet Need

ALS is a relentless neurodegenerative syndrome of the human motor neuron system, for which no curative treatment exists. It is characterized by significant variability in progression rates posing a major challenge for patient stratification in clinical trials. Ideal ALS biomarkers should remain stable during the course of the disease, be detectable in an accessible tissue, and be easily measurable. To date, intensive research has identified only a few potential blood-based ALS biomarkers, including cell-free neurofilaments, pro-inflammatory cytokines, and NfL. Additional markers are needed to improve stratification, facilitate the clinical trial design and enroll patients into clinical cohorts with reduced phenotypic variability. miRNAs are small, non-coding RNAs that are essential for motor neuron survival and have been shown to be globally downregulated in postmortem ALS motor neurons. While circulating miRNA profiles have been previously characterized in ALS, the potential of miRNA biomarkers for ALS prognosis and as readouts of disease progression is yet unknown.

The Solution

Prof. Eran Hornstein and his team developed novel methods of assessing prognosis and disease progression in ALS with circulating cell-free miRNAs[1].

Technology Essence

Prof. Hornstein and his team applied unbiased next-generation sequencing to investigate the potential of plasma cell-free microRNAs as biomarkers of ALS prognosis in 252 patients with detailed clinical phenotyping. First, they identified miRNAs with stable plasma levels throughout the disease course in a longitudinal cohort of 22 patients. Next, they demonstrated that high levels of miR-181, a miRNA enriched in neurons of the brain and spinal cord, predict a >2-fold risk of death in the discovery cohort (126 patients) and an independent replication cohort (additional 122 patients). Lastly, the team has shown that miR-181 measurement enhances the prognostic value of NfL, enabling the joint miRNA-protein measure to compute prognosis more precisely than any of the circulating biomolecules on their own.

Applications and Advantages

- Predicts ALS prognosis
- Minimally invasive biomarker for follow-up of disease progression
- May serve as a pharmacodynamic biomarker for monitoring ALS drug effects
- Effective biomarker for ALS clinical trial endpoints
- Reduces trial size length and overall expenses
- Can be combined with NfL for superior prognostic accuracy

Development Status

Prof. Hornstein and his team discovered that miR-181 can predict ALS progress. Furthermore, miR-181 performance was comparable with the established NfL biomarker and when combined, miR-181+NfL established a novel RNA-protein biomarker pair with superior prediction capacity of ALS prognosis. This was validated on a large cohort of ALS patient, and it is ready to be deployed as a prognostic tool in ALS clinical trials.

References

Magen I, Yacovzada NS, Yanowski E, et al. Circulating miR-181 is a prognostic biomarker for amyotrophic lateral sclerosis. *Nat Neurosci*. 2021;24(11):1534-1541. doi:10.1038/s41593-021-00936-z [1]

Patent Status

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