Washington University in St. Louis
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MICRORNA BIOMARKER AND DRUG TARGET FOR ALS AND OTHER MOTOR NEURON DISEASES

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Prof. Timothy Miller and colleagues have identified a motor neuron-specific, drug responsive microRNA (miR-218) that reflects the pathology of amyotrophic lateral sclerosis (ALS). This biomarker could be a target for therapeutic intervention or a proxy for motor neuron health and survival, including early diagnosis/detection of ALS and monitoring efficacy in clinical trials for ALS drugs.

ALS is a disorder marked by the progressive loss of motor neurons. Early diagnosis of the disease and its progression could facilitate earlier treatment to slow degeneration. In addition, robust, quantitative surrogate markers are necessary for evaluating much-needed ALS therapies in development. miR-218 is a biomarker that could fill that need with the potential to provide early, accurate detection and ongoing monitoring of progression and therapeutic efficacy. This miRNA is dramatically increased in patients with ALS compared to controls, providing a direct readout of motor neuron health (the underlying pathology of ALS). Also, rodent studies demonstrated miR-218 responsiveness to ALS therapy and a mechanistic link to excitotoxicty in nearby astrocytes. These findings indicate that miR-218 could enable the discovery and assessment of drugs for ALS and other motor neuron diseases as a target, a diagnostic or a surrogate marker in clinical trials.

Stage of Research

- **Identification in mice** – The inventors found that miR-218 levels tracked with motor neuron loss and disease progression. In addition, these levels were responsive to an ALS therapy in rodent models of ALS.
- **Validation in humans** – The inventors found miR-218 is highly increased in the cerebrospinal fluid of patients with ALS vs. healthy controls.
- **Mechanistic studies** – The inventors established the pathogenic mechanism that links dying motor neuron-derived miRNAs with astrocyte dysfunction. Specifically, miR-218 can be taken up by nearby astrocytes and down-regulate glutamate-related excitotoxicity. Antisense oligonucleotides that inhibit miR-218 in a mouse model of ALS mitigates these changes.

Applications

- **Biomarker** for ALS and other motor neuron diseases
  - clinical trials - monitor efficacy of therapeutic candidates
  - diagnostics - early detection and monitoring disease progression
- **Drug target** – identify drugs that treat ALS by blocking miR-218 activity

Key Advantages

- **Dynamic marker:**

    - responsive to drug treatment
    - levels change with disease progression
- **Early detection:**
    - motor neuron-specific to potentially identify the loss and pathology that define the onset of disease
    - could facilitate early treatment to slow degeneration

Publications

- Hoye M.L., Regan M.R, Jensen L.A., Lake A.M.,…..Dougherty J.D., Miller T.M (2018), Motor neuron-derived microRNAs cause astrocyte dysfunction in amyotrophic lateral sclerosis, *Brain* 141(9):2561-2575
- Hoye, M. L., Koval, E. D., Wegener, A. J., Hyman, T. S., Yang, C., O'Brien, D. R., ... & Kunikata, T. (2017). MicroRNA profiling reveals marker of motor neuron disease in ALS models. *Journal of Neuroscience*, 37(22), 5574-5586.

Patents:

- Methods to detect motor neuron disease comprising micro-RNAs (U.S. Patent No. 10,487,324)
- Additional patent application pending

Website

- Miller lab