April 2021 - MND Research Article summary – Anushka Bhargava, PhD student, University of Sheffield

**A prolonged study following ALS patients found circulating biomarkers in the blood that can define disease prognosis and progression in ALS patients**

*Dobrowolny, G., Martone, J., Lepore, E. et al. A longitudinal study defined circulating microRNAs as reliable biomarkers for disease prognosis and progression in ALS human patients. Cell Death Discov. 7, 4 (2021) DOI: [https://doi.org/10.1038/s41420-020-00397-6](https://doi.org/10.1038/s41420-020-00397-6)*

Amyotrophic Lateral Sclerosis (ALS) is a fatal disorder that causes the loss of neurons responsible for controlling voluntary muscle movement, which includes chewing, walking, and even breathing. This loss leads to muscle wasting, paralysis, and eventual death due to failure to breathe. It is a progressive, multifactorial, and multisystemic disorder that cannot be cured or slowed significantly. Due to the complexity of the disease mechanism, the progression of the disease is highly variable, proceeding in affected individuals with different aggressiveness and velocity.

A biomarker can be defined as a naturally occurring molecule, gene, or characteristic by which a particular disease can be identified. There is a large need to find biomarkers in patients to indicate specific disease, disease stage, and severity of the disease. Ideally, these makers need to be easily detected from blood, saliva, urine, or CSF (colourless bodily fluid found in the brain and spine), so they can be easily and repeatedly monitored in patients. Over the last two decades, intensive work has been carried out to find consistent biomarkers for ALS. Several candidates have been explored, but, unfortunately, none of the biomarkers have been translated into a practical diagnostic tool. This study overcomes this limitation by examining the levels of circulating microRNAs in the blood of ALS patients during disease progression.

MicroRNAs (miRNAs) are a type of nucleic acid molecules (main information-carrying molecules of the cell) that have been highly conserved throughout evolution across species. Nucleic acids are usually long and are responsible for producing a cell’s action molecules called proteins, however, miRNAs are short-length molecules that are not responsible for the production of proteins. Their normal levels in the body are frequently altered in human disease. Many tissue-specific miRNAs are released into the blood under disease conditions, thus there is an increasing interest to define their role in the development of several degenerative diseases, as they are easy to collect as samples from patients and low-cost potential disease biomarkers. Recent studies in ALS have reported the identification of potential circulating miRNAs as putative biomarkers for ALS diagnosis. In this study, the authors followed healthy and ALS patients over a long period to define a potential miRNA signature for ALS progression. They analyzed circulating levels of five specific miRNAs in the blood from ALS patients, collected every 3 months for a maximum of 30 months of follow-up.
The levels of five selected miRNAs (miR-206, miR-133a, miR-151a-5p, miR199a-5p, and miR423–3p) were analyzed during the disease progression in each patient. It was observed that high levels of miR-206, miR-133a, and miR-151a-5p could predict a slower clinical decline of patient functionality and therefore highlight a better prognosis and slower progression of the disease. MiR-206 and miR-151a-5p blood levels were significantly higher at the mild stage of ALS, decreasing in the moderate and severe stages of ALS. On the other hand, the expression levels of miR-133a and miR-199a-5p remained low throughout the disease, showing a diagnostic significance in moderate and severe stages for miR-133a and in mild and terminal ones for miR-199a-5p. Moreover, miR-423–3p and 151a-5p were significantly low respectively in mild and terminal stages of the disease. They also observed that low levels of miR-199a-5p and miR-423-3p are hallmarks of the early phases of ALS. Overall, the data suggests that these miRNAs represent potential prognostic biomarkers for ALS disease.

The novelty of this study stands in the fact that it is the first to perform absolute quantification of circulating miRNAs in ALS patients, providing a cut-off threshold to discriminate slow progressive patients from fast progressive ones. Moreover, this work is the first to perform a longitudinal study that evaluates miRNAs levels during the progression of the disease of each patient, giving the analyzed miRNAs the power to define the likely disease course of ALS. With this study, they overcome the limitation related to the absence of an ALS biomarker that can predict disease progression, diagnosis, and prognosis rather than just discriminate normal from disease conditions.

[1] Gene: A gene is the basic physical and functional unit of heredity that can be passed on from parent to offspring.