Clinical Care Hindered by Subjective “Measurements”

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that destroys both upper and lower motor neurons. As a result, patients experience progressive voluntary muscle action loss and fatal respiratory failure within a few years of onset. Only 10% of cases are considered hereditary. There is no known cure for this disease, and the discovery of any disease reversing treatment is hampered by a lack in understanding of the disease along with the lack of an objective and linear measure of disease progression. The ALS-Functional Rating Scale (ALS-FRS) (Figure 1) is currently the most widely used clinical measure. This 12-question and 48-point survey assesses one’s ability to perform everyday activities. A quantitative measurement is sorely needed. In this work, we investigate the efficacy of peptide measurements in cerebrospinal fluid (CSF) of ALS to be accurate signatures in modeling disease progression.

ALS Functional Rating Scale: Current gold standard for evaluating therapeutic efficacy in clinical trials

Dyspnea (shortness of breath)

• None
• Occurs when walking
• Occurs with one or more: eating, bathing, dressing
• Occurs at rest, either sitting or lying
• Significant difficulty, considering mechanical support

Salivation

• Normal
• Slight, but definite excess of saliva in mouth, with or without drooling
• Moderately excessive saliva, may have drooling
• Marked excessive saliva with some drooling
• Marked drooling, requires constant tissue

Longitudinal Proteomic Analysis of ALS Patient CSF

Figure 3. Experimental design for analysis of longitudinal CSF. 63 samples and one digestion quality control sample each day were split between three days of digestion and randomized before analysis sequencing within digestion day. Gas-phase fractionated injections for chromatogram library building were collected in the middle of the experiment.

Data Quality Control and Patient Variability

Figure 4. A: Boxplots of logpeptide abundances measured in every sample to visualize data quality. One outlier sample is clear, and this patient was excluded from most subsequent analyses. B: Principal component analysis separating peptide abundances of samples. C: Boxplots of variation both within and among patient and QC samples.

Targeted Global Inflammation Index

Figure 5. Global inflammation changes were studied by taking the median peak of peptides from inflammatory proteins and calculating the percent change in those medians from each patient’s baseline collection visit. This was plotted against the rate of disease progression in each patient, defined as the ratio of the change in score over the change in time between collections.

Conclusions and Future Work

• We have shown the efficacy of proteomics in longitudinal sampling to quantitatively model disease progression in ALS patients.
• A targeted study of peptides used in the model within an independent cohort of ALS patients should be investigated for further validation of this study.

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Investigation of Protein Signatures Associated with ALS Disease Progression Using Data Independent Acquisition Mass Spectrometry

Allyson L. Mellinger, Emily H. Griffith, and Michael S. Bereman

1Department of Chemistry, 2Department of Statistics, and 3Department of Biological Sciences North Carolina State University, Raleigh, NC