

# PATsmart™ ZipChip® System: Metabolite Profiling Reveals Predictive Biomarkers and the Absence of $\beta$ -Methyl Amino-L-alanine in Plasma from Individuals Diagnosed with Amyotrophic Lateral Sclerosis

Technical Note

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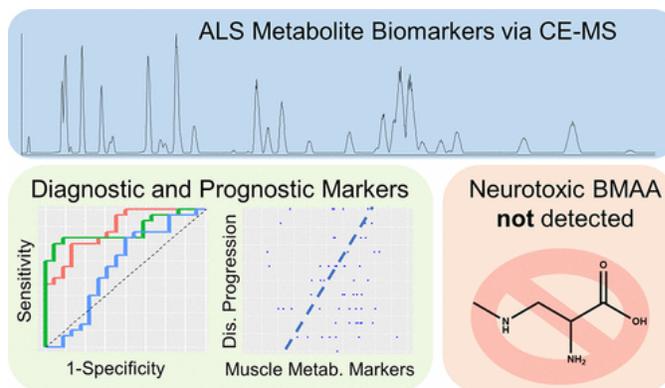
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## Abstract

By employing chip-based capillary zone electrophoresis coupled to high-resolution mass spectrometry, we profiled the plasma metabolome of 134 patients diagnosed with sporadic amyotrophic lateral sclerosis (ALS; 81 males and 53 females) and 118 individuals deemed healthy (49 males and 69 females). The most significant markers ( $p < 0.01$ ) were creatine, which was 49% elevated, and creatinine and methylhistidine, which were decreased by 20 and 24%, respectively, in ALS patients. The ratio of creatine versus creatinine increased 370 and 200% for male and female ALS patients, respectively. In addition, male ALS patients on average had 5 – 13% lower amounts of seven essential amino acids, whereas females did not significantly differ from healthy controls. We developed two models using the metabolite abundances: (1) a classification model for the separation of ALS and healthy samples and (2) a classification model for the prediction of disease progression based on the ALS functional rating score. Utilizing a Monte Carlo cross-validation approach, a linear discriminant analysis model achieved a mean area under the receiver operating characteristic curve (AUC) of 0.85 (0.06) with a mean sensitivity of 80% (9%) and specificity of 78% (10%) for the separation of ALS and controls, respectively. A support vector machine classifier predicted progression categories with an AUC of 0.90 (0.06) with a mean sensitivity of 73% (10%) and a specificity of 86% (5%). Lastly, using a previously reported assay with a stable isotope labeled ( $^{13}\text{C}_3$   $^{15}\text{N}_2$ ) spike-in standard, we were unable to detect the exogenous neurotoxic metabolite,  $\beta$ -methylamino-L-alanine, in the free or protein-bound fraction of any of the 252 plasma samples.



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