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ZipChip

Metabolite Profiling Reveals Predictive Biomarkers and the Absence of β-Methyl Amino-L-alanine in Plasma from Individuals Diagnosed with Amyotrophic Lateral Sclerosis

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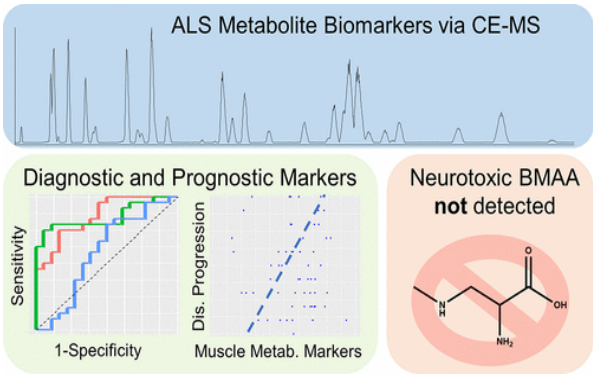
ABSTRACT: By employing chip-based capillary zone electrophoresis coupled to high-resolution mass spectrometry, we profiled the plasma metabolome of 134 patients diagnosed with sporadic amyotrophic lateral sclerosis (ALS) (81 males and 53 females) and 118 individuals deemed healthy (49 males and 69 females). 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 an 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 ($^{13}C_3{}^{15}N_2$) spike-in standard, we were unable to detect the exogenous neurotoxic metabolite, β-methylamino-l-alanine, in the free or protein-bound fraction of any of the 252 plasma samples.



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