A Potential Role of Urinary p75ecd as a Biomarker for Amyotrophic Lateral Sclerosis in an American Cohort

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Background: Neurological disorders present a unique complexity compared to other diseases, involving multiple risk factors, causes, treatments, and outcomes. These disorders often exhibit various molecular and morphological changes indicative of disruptions in cellular plasticity and resilience. The pathogenesis of many neurological disorders remains unclear, necessitating ongoing investigations. Amyotrophic lateral sclerosis (ALS) exemplifies an idiopathic and fatal neurodegenerative disease marked by the degeneration of upper and lower motor neurons. The average life expectancy post-diagnosis is a mere 36 months, primarily attributed to respiratory muscle denervation.The persistent challenges in ALS clinical trials and the absence of effective therapeutic options have intensified interest in the potential role of biomarkers in advancing therapy development. Notably, neurofilament light (NfL) and phosphorylated neurofilament heavy (pNfH), cytoskeletal proteins in biological fluids, emerge as promising prognostic markers and potential pharmacodynamic biomarkers. However, their relatively stable levels over time limit their utility in reflecting disease progression. Consequently, a significant gap exists in identifying biological fluid-based biomarkers for monitoring disease progression. In response to this gap, our focus turns to the common neurotrophin receptor, p75, as a potential biomarker for motor neuron degeneration. Building on existing literature revealing elevated levels of the extracellular domain of p75 (p75ecd) in the urine of ALS patients compared to healthy individuals, we explore the potential of urinary p75ecd as a novel biomarker for disease progression and prognosis within an American cohort.

Methods: The study included samples from ALS patients and healthy controls. The urine samples of 60 confirmed ALS patients were purchased from ‘National ALS biorepository’. The urine samples of 19 healthy controls were collected from friends, family, and colleagues on volunteer basis. The samples were collected and procured according to the IBC and IRB guidelines respectively. Each sample was tested in triplicate, to quantify p75ecd levels by sandwich ELISA and to quantify creatinine by colorimetric enzymatic assay. Levels of urinary p75ecd were standardised to urinary creatinine and data comparisons between two groups were performed using the Unpaired t test test for two independent groups.

Result: p75ecd was higher in patients with ALS (9.229 ± 1.198 ng/mg creatinine; N=60) compared to controls (3.979 ± 0.2891 ng/mg creatinine; N=19, p value: 0.0083).

Conclusion: The assay for urinary p75ecd demonstrates strong analytical robustness, signaling its potential as a promising biomarker for Amyotrophic Lateral Sclerosis (ALS) with applications in prognosis, disease progression monitoring, and potential pharmacodynamic assessments. Notably, urinary p75ecd stands out as a biomarker offering valuable prognostic insights and holds

the unique distinction of being the sole biological fluid-based indicator of disease progression in ALS.