

Title: Role of E121K mutation of D-Amino Acid Oxidase in Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal neuromuscular disorder, and our research group has been investigating this condition. In this report, we focused on a rare and novel mutation E121K in DAO found by our group in ALS patients from India to better understand the disease's pathogenesis. DAO is a peroxisomal enzyme responsible for degrading D-amino acids, and dysfunctional DAO disrupts D-serine regulation, leading to the degeneration of motor neurons. Our study employed computational, biophysical, and cellular approaches to understand disease mechanisms. E121K DAO showed altered dynamics, reduced cofactor binding, and increased aggregation propensity. Cellular experiments revealed mutant protein aggregates, cell morphology changes, and neuronal cell death. Autophagy imbalance due to aggregation increased p62, OPTN, and LC3II levels, promoting cell death. Our findings offer insights into ALS pathogenesis caused by the E121K mutation.