ALS-associated p62 mutations alter TDP-43 solubility and localization in a cell culture model of disease

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that causes motor function loss. TDP-43 is a DNA-binding protein that serves many important roles such as a transcription factor and in RNA processing. Its abnormal aggregation is a hallmark of disease. Additionally, its mis-localization to the cytoplasm has also been linked to disease. p62 is a scaffold protein and single point mutations in the gene have been found in patients with disease. TDP-43 variants were co-expressed with mutant p62 variants among different domains of the gene in HEK293 cells. Solubility of TDP-43 was determined by fractionation and Western blotting. Immunofluorescence was used to provide further data on TDP-43 aggregation and localization within the cell. Data showed that TDP-43 solubility alters by forming aggregates in some mutants. Further, localization of TDP-43 alters with the different p62 mutants to either the nucleus or the cytoplasm. Thus, specific mutants and domain regions of the p62 gene have shown varying outcomes in mis-aggregation and mis-localization of TDP-43.