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OHSU discovery may lead to new treatment for ALS

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Researchers at Oregon Health & Science University School of Dentistry have discovered that TDP-43, a protein strongly linked to ALS (Amyotrophic Lateral Sclerosis) and other neurodegenerative diseases, appears to activate a variety of different molecular pathways when genetically manipulated. The findings have implications for understanding and possibly treating ALS and neurodegenerative diseases such as Alzheimer's and Parkinson's.

ALS affects two in 100,000 adults in the United States annually and the prognosis for patients is grim.The new discovery is published online in *G3: Genes, Genomes, Genetics* (and the July 2012 print issue of G3).

Using a fruit fly model, the OHSU team genetically increased or eliminated TDP-43 to study its effect on the central nervous system. By using massively parallel sequencing methods to profile the expression of genes in the central nervous system, the team found that the loss of TDP-43 results in widespread gene activation and altered splicing, much of which is reversed by rescue of TDP-43 expression. Although previous studies have implicated both absence and over expression of TDP-43 in ALS, the OHSU study showed little overlap in the gene expression between these two manipulations, suggesting that the bulk of the genes affected are different.

"Our data suggest that TDP-43 plays a role in synaptic transmission, synaptic release and endocytosis," said Dennis Hazelett, Ph.D., lead author of the study. "We also uncovered a potential novel regulation of

several pathways, many targets of which appear to be conserved."

Provided by Oregon Health & Science University