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HUMAN MUTATIONS LINKED TO EPILEPSY ALTER SYNAPTIC VESICLE FUSION IN *C. ELEGANS*

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Abstract: The SNAP-25 portion of the SNARE (Soluble NSF Attachment Protein REceptor) complex binds to synaptotagmin- 1 (snt-1), a calcium ion sensing protein, to facilitate synaptic vesicle fusion and neurotransmitter release. Researchers have identified mutations to specific regions of SNAP-25 and snt-1 that cause neurological disorders, including epilepsy and intellectual disability, in human patients. The exact mechanisms of disease in these patients are unknown. We hypothesize some of these mutations disrupt the primary binding interface between SNAP- 25 and snt-1. Therefore, we aim to understand how these mutations affect neurotransmission and cause disease. We also aim to extend this understanding to describe snt-1's repressive functions. Here, we used CRISPR/Cas9 to develop disease models in *C. elegans*. We used these models to determine how each mutation changes the rates of neurotransmission. We identified a hydrophobic region along the binding interface between SNAP- 25 and snt-1, where mutations resulted in increased rates of neurotransmitter release. We also identified a hydrophilic region at this interface, where mutations resulted in decreased rates of neurotransmitter release. We postulated that snt-1 binds at these regions to perform a repressive role. Mutations of interest at the hydrophobic region weaken snt-1 binding, decreasing repressive function, while mutations of interest at the hydrophilic region strengthen snt-1 binding, increasing repressive function. These findings will help physicians make more informed decisions regarding patient therapies that target increased or decreased neurotransmission rates. Furthermore, the findings presented here increase the basic scientific understanding of synaptotagmin-1, its interactions with SNAP-25, and mechanisms by which these mutations cause disease.