Angelman Syndrome is a neurological disorder associated with severe mental and motor impairments [1]. It is known that *SNRPN* is expressed at high levels in neurons, and is involved in RNA processing [2] Dysfunctional RNA processing in neurons can lead to neurodegeneration, which can cause epilepsy [3][4]. Certain patients with Angelman Syndrome experience epilepsy, although the cause of variation in phenotypes between cases is unknown. About 10% of patients with Angelman Syndrome have a deletion in SNRPN, possibly disrupting its functional role in neurons [5]. This may explain why only certain patients with Angelman Syndrome experience epilepsy. This deletion may lead to an inactive or aberrant form of SNRPN, affecting proper splicing in neurons, possibly leading to neurodegeneration.  Although the function of *SNRPN* in RNA processing has been extensively characterized, it is unknown if it has a role in neurodegeneration, leading to epilepsy.

My **primary goal** is to determine the role of *SNRPN* in epilepsy.

My **hypothesis** is that *SNRPN* mutants have obstructed splicing abilities, producing neurotoxic RNA isoforms that lead to neurodegeneration, causing ataxia in Angelman Syndrome patients.

My **long-term goal** is to elucidate what collection of preRNAs require SNRPN to properly process them in neurons.

**Aim 1:** Determine if improper SNRPN function leads to neurodegeneration.

**Approach:** I will use CRISPR to knockout the Sm domain in SNRPN and compare the phenotypes between wild type and *SNRPN* mutant rats.

**Rationale:** The Sm domain of SNRPN is implicated in RNA binding. If this domain is nonfunctional, the RNA processing by SNRPN will be obstructed, possibly leading to neurodegeneration. **Hypothesis:** Inhibiting the function of the Sm domain will prevent proper splicing from occurring because SNRPN will not be able to bind RNA.

**Aim 2:** Determine if *SNRPN* mutants express alternative RNA isoforms in neurons.

**Approach:** I will use RNA-Seq to analyze the potential differential expression of neuronal transcripts between wild type and mutants, searching for neurotoxic isoforms.

**Rationale:** RNA-Seq will determine if there is enrichment for alternate transcript forms in *SNRPN* mutants compared to wild type control. If differential expression is evident, it indicates that *SNRPN* mutations are responsible. Furthermore, if the transcripts enriched in *SNRPN* mutants are neurotoxic, it may indicate that *SNRPN* mutations are involved in the manifestation of neurodegeneration.

**Hypothesis:** Since SNRPN is implicated in RNA processing, SNRPN mutants will be enriched for alternate splice forms of transcripts compared to those in wild type.

**[1]** Angelman Syndrome: Genetics Home Reference

[<https://ghr.nlm.nih.gov/condition/angelman-syndrome>](https://ghr.nlm.nih.gov/condition/angelman-syndrome)

**[2]** Li, H., Zhao, P., Xu, Q., Shan, S., Hu, C., Qiu, Z., & Xu, X. (2016). The autism-related gene SNRPN regulates cortical and spine development via controlling nuclear receptor Nr4a1. *Scientific Reports,* *6*, 29878. doi:10.1038/srep29878

<https://www.ncbi.nlm.nih.gov/pubmed/1533223>

**[3]** Neuropathology: An illustrated interactive course for medical students and residents [<http://neuropathology-web.org/chapter9/chapter9hAtaxia.html>](https://academic.oup.com/hmg/article/8/2/337/585544/The-Chromosome-15-Imprinting-Centre-IC-Region-Has)

**[4]** Gallo, J. . (2005). The role of RNA and RNA processing in Neurodegeneration. *Journal of Neuroscience*, *25*(45), 10372–10375. doi:10.1523/jneurosci.3453-05.2005

< http://www.jneurosci.org/content/25/45/10372 >

**[5]** Farber, C. (1999). The chromosome 15 imprinting centre (IC) region has undergone multiple duplication events and contains an upstream exon of SNRPN that is deleted in all Angelman syndrome patients with an IC microdeletion. *Human Molecular Genetics*, *8*(2), 337-343. doi:10.1093/hmg/8.2.337

<https://academic.oup.com/hmg/article/8/2/337/585544/The-Chromosome-15-Imprinting-Centre-IC-Region-Has>