Angelman Syndrome is a neurological disorder associated with severe mental and motor impairments, such as ataxia, a movement disability [1][2]. It is known that *SNRPN* is expressed at high levels in neurons, and is involved in RNA processing [3] Dysfunctional RNA processing in neurons can lead to neurodegeneration, which can cause ataxia [4][5]. About 10% of patients with Angelman Syndrome have a deletion in SNRPN, possibly disrupting its functional role in neurons [6]. Although the function of *SNRPN* in RNA processing has been extensively characterized, it is unknown if it has a role in neurodegeneration, leading to ataxia.

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

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.

**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:** If differential expression is evident, it indicates that SNRPN mutations are responsible.

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

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

**[2]** National Ataxia Foundation

<http://www.ataxia.org/learn/ataxia-diagnosis.aspx>

**[3]** 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>

**[4]** 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)

**[5**] 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 >

**[6]** 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

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