Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neuropsychological disorders diagnosed broadly characterized by individuals who have difficulty paying attention, controlling impulse behavior, and hyperactivity (1). ADHD is known to have a strong genetic component with large scale twin studies showing heritability to be from anywhere 75-91% (2). LPHN3 is one gene with known variants expressed in ADHD patients. LPHN3, is a G protein-coupled receptors almost exclusively expressed in the brain. Several human patients with LPHN3 mutations have reduced formation in synapse density (3). However, it is unknown if synapses can be recovered using commonly prescribed ADHD medication.

My **long-term goal** is to determine how LPHN3 variants can be treated to increase neural synapses.

I **hypothesize** that LPHN3 mutants will have synaptic function recovered with stimulant medications.

**Specific Aim #1: Determine if synapses in LPHN3 mutants can be recovered with common stimulant medication.**

***Approach***: Remove the hormone receptor domain in *danio rerio* with CRISPR-Cas9. I will use δL to measure synapses; pre stimulant treatment versus post treatment. I will also use use a control that has a functioning hormone receptor domain. I will then look for changes in synapses between the two groups.

***Rationale***: Methylphenidate and amphetamine are two widely used stimulants used to target dopamine receptors, which are also G protein receptors. LPHN3 is also a G protein receptor and could also be a target of

***Hypothesis***: Stimulant drugs specific for targeting dopamine receptors will be effective in increasing synapses in LPHN3 without hormone receptor domains.

Using zebrafish as a model to study ADHD. It is a good choice because LPHN3 is highly conserved among humans and zebrafish. Brain morphology is very similar between zebrafish and mammals, and contain major neurological systems such as: neurotransmitter receptors, transporters, and enzymes for synthesis and metabolism. They are also sensitive to neurotropic drugs. ADHD-like behaviors are also easily observed. (5)

References

1. https://www.cdc.gov/ncbddd/adhd/facts.html
2. Levy F, Hay DA, McStephen M, et al. Attention-deficit hyperactivity disorder: a category or a continuum? Genetic analysis of a large-scale twin study J Am Acad Child Adolesc Psychiatry. 1997;36:737-44
3. Acosta, M. T., Swanson, J., Stehli, A., Molina, B. S. G., the MTA Team, Martinez, A. F., Arcos-Burgos, M. and Muenke, M. (2016), *ADGRL3 (LPHN3)* variants are associated with a refined phenotype of ADHD in the MTA study. Mol Genet Genomic Med, 4: 540–547. doi:10.1002/mgg3.230
4. Deeann Wallis, Denise S. Hill, Ian A. Mendez, Louise C. Abbott, Richard H. Finnell, Paul J. Wellman, Barry Setlow, Initial characterization of mice null for Lphn3, a gene implicated in ADHD and addiction, Brain Research, Volume 1463, 29 June 2012, Pages 85-92, ISSN 0006-8993,
5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3913794/