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**Attention Deficit Hyperactivity Disorder and the LPHN3 gene: Specific Aims**

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neuropsychological disorders diagnosed. It is 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 anywhere from 75-91% (2). LPHN3, an adhesion G-protein coupled receptor, is almost exclusively expressed in the brain. Loss in synaptic density has been identified in zebrafish whow have a loss of function mutation in LPHN3, and patients with known LPHN3 variants (3). Common ADHD medication has been shown to recover behavioral phenotypes in zebrafish (4). However little is known as to what domains are involved in synaptic density in LPHN3.

My **primary goal** is to better understand how LPHN3 plays a role in neurological synaptic density. I **hypothesize** that specific domains in LPHN3 are important in synaptic density. My **long-term goal** is to discover a new way to treat ADHD patients with mutant LPHN3.

**Specific Aim #1**: **Identify the domains in LPHN3 that influence synaptic density.**

***Rationale***: Synaptic density is important for neuron communication and individuals with ADHD have significantly less synaptic density than unaffected individuals. Discovering which domains influence synaptic density will help understand how mutant forms of LPHN3 can cause ADHD.

***Approach***: Using Clustal Omega, SMART, and PFAM I will identify conserved domains among zebrafish and humans in LPHN3. Then, using CRISPR-Cas9, I will remove each conserved domain identified. The synaptic density will then be measured in mutant zebrafish, by immunoprecipitation of PSD-95 from brain tissue.

***Hypothesis***: I predict that the hormone receptor domain will have the greatest affect on synaptic density as current ADHD stimulant medication target neurotransmitter transporter proteins.

**Specific Aim #2**: **Discover small molecules that can recover synaptic density in LPHN3 mutant domains previously identified.**

***Rationale***: Small molecules are currently being used to treat ADHD patients. Identifying small molecules specific to recovering synaptic density in LPHN3 could lead to new treatments.

***Approach***: Use a chemical genetic screen to discover small molecules that can bind to LPHN3 domains involved with synaptic density.

***Hypothesis***: Synaptic density can be recovered by small molecules that target domains in the extracellular region such as the hormone receptor.

References

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