Hepatic Lipase Deficiency (HLD) is an autosomal recessive disorder that is characterized by elevated triglyceride and cholesterol levels in the blood of affected patients [1, 2]. HLD is caused by mutations in Lipase C gene (LIPC) which encodes the enzyme hepatic lipase (HL). Hepatic lipase is predominantly involved in the conversion of intermediate-density lipoproteins into low-density lipoproteins and triglyceride-rich high-density lipoproteins (HDL) found during the well-fed state into triglyceride-poor HDL found in the fasting state [2].

Several mutations have been identified as pathogenic for hepatic lipase deficiency *however there may be unknown mutations that cause varying degrees of hepatic lipase deficiency in the population*. Detailing the effects of LIPC mutations in model organisms will help identify people with less prominent forms of hepatic lipase deficiency who may require treatment to manage disease symptoms.

The **long-term goal** of this project is to improve genetic testing for hepatic lipase deficiency. The **goal** of this specific project is to identify currently unknown variants involved in hepatic lipase deficiency. As most of the current data comes from sequencing of already diagnosed patients, my **hypothesis** is that there are many LIPC variants that yield less severe forms of HLD that go undiagnosed and therefore not identified as pathogenic mutations. *Danio rerio* will be used as a model organism due to their short life cycles, the presence of two ortholog genes with high similarity to human LIPC, and the presence of established models for dyslipidemia research [3].

**AIM 1: Identify novel LIPC mutations that contribute to HLD-like phenotypes.**

**Approach:** I will perform a forward genetic screen for Danio rerio mutants that have elevated triglyceride and high-density lipoprotein cholesterol levels, similar to those seen in human hepatic lipase deficiency. Once identified, these mutants can be genotyped. Those with mutations in lipca, the LIPC ortholog in Danio rerio, can be further compared to other ortholog sequences to infer what part of the protein or process is disrupted by the mutation.

**Rationale:** Identification of mutations that cause a similar phenotype in Danio rerio will lend insights into mutations that contribute to hepatic lipase deficiency in humans, but are currently unknwon.

**Hypothesis:** Several mutations will be found that cause a less severe form of hepatic lipase deficiency. It is also possible that this forward genetic screen may implicate other genes involved in lipid metabolism that contribute to the hepatic lipase phenotype.

**References**

[1] Ng, D. M., Burnett, J. R., Bell, D. A., Hegele, R. A., & Hooper, A. J. (2019). Update on the diagnosis, treatment and management of rare genetic lipid disorders. Pathology, 51(2), 193-201. doi:10.1016/j.pathol.2018.11.005

[2] Kobayashi, J., Miyashita, K., Nakajima, K., & Mabuchi, H. (2015). Hepatic Lipase: A Comprehensive View of its Role on Plasma Lipid and Lipoprotein Metabolism. Journal of Atherosclerosis and Thrombosis, 22(10), 1001-1011. doi:10.5551/jat.31617

[3] Schlegel, A. (2016). Zebrafish Models for Dyslipidemia and Atherosclerosis Research. Frontiers in Endocrinology, 7. doi:10.3389/fendo.2016.00159