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Specific AIMs

Alpers-Huttenlocher Syndrome (AHS) is a severe neurological disorder that also affects other parts of the body. AHS is known for having seizures that can often lead from one seizure to another. The disease affects 1 in 100,000 to 250,000 and 80% of individuals present symptoms within the first two years of their lives. The disease progressively destroys the individuals cognitive function, often debilitating an individual's motor skills. However the usual cause of death is often liver failure. The gene POLG (aka POLG1) is a major contributor to a multitude of genetic diseases and the most severe is Alpers-Huttenlocher Syndrome. The POLG gene encodes the α (alpha) subunit of the protein polymerase γ (gamma). This protein is necessary for mitochondria to replicate mitochondrial DNA (mtDNA), which is used to encode genes used in the mitochondria for energy production. POLG mutations can cause non functionality in the α subunit which leads to problems with mtDNA replication. Often mtDNA replication results in a decreased amount of functionable mtDNA which leads to a drop in the amount of energy the cell receives due to the mitochondria not receiving the correct proteins it needs for energy production that results from this. Although we know the phenotype caused by the POLG mutations, we do not know the physical affects the mutations have on the alpha subunit protein that causes disorder in normal function. Insight into this could lead to treatments of this disease as well as many other diseases associated with this gene.

**My goal** is to obtain a better and more complete understanding of the effects of the POLG gene on the mitochondria and the human body overall. We will test our hypothesis that POLG mutations cause a misfolding of the α subunit protein so that it becomes non functioning and unsuccessful in binding to the other proteins involved in the DNA polymerase complex in the mitochondria.

• Identifying molecules that interact with the protein is extremely useful in determining the reasons we have our disease phenotype. One such way we can test this is through **Small Molecule assays**. We hope to find that certain small molecules cause a conformational change in our protein that causes a disruption in protein binding. By determining what small molecules interact with our α subunit we may better understand the cause of its ineffectiveness within the mtDNA replication complex.

• We will study the protein interactions within the protein polymerase γ and how they will affect the function of mtDNA replication. Specifically we will look at the α subunit by using **Tap-tag assays** paired with **Mass Spectrometry.** We will use this to determine if in a mutated protein we observe different protein interactions than in a wt protein.These are useful for confirming the existence of a protein-protein interactions as well as finding new protein interactions.

This project will help us better understand Alpers-Huttenlocher syndrome and possibly lead us to more effective treatments and a better understand of the mitochondria as a whole. Along with this disease we will also be able to better understand other disorders associated with the POLG1 gene.

*References*

*• "POLG Gene." Genetics Home Reference. N.p., 23 Feb. 2015. Web. 26 Feb. 2015.*

*• "Human Molecular Genetics." Mitochondrial DNA Polymerase-γ and Human Disease. Oxford Journals, 2006. Web. 26 Feb. 2015.*

*• "Correlative Light- and Electron Microscopy with Chemical Tags." Sciencedirect.com. Journal of Structural Biology, May 2014. Web. 26 Feb. 2015*

*• "Pull-Down Assays." Pull-Down Assays. N.p., n.d. Web. 26 Feb. 2015.*