Genetics 564
Specific Aim Draft #1
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Optic atrophy type 1 is a genetic disease caused by a mutation within the OPA1 gene [1]. The function of the OPA1 gene is to provide instruction to produce the OPA1 protein [2]. This protein can be found mainly in the eye, which is the retinal ganglion cells, and it is responsible for maintaining the structure of mitochondria [3]. The mutation misshapes the mitochondria and further affects the function of retinal ganglion cells [5]. With the dysfunction of mitochondria, cells that are contained in the optic nerves, such as the retinal ganglion cells, will lead to apoptosis [4]. As the cell dies, it becomes impossible for optic nerves to transmit visual signals, and this eventually leads to optic atrophy type 1 [6]. It is **known** that patients with optic atrophy type 1 will experience blindness, blocked vision, or color vision deficiency [2]. Also, the OPA1 gene undergoes autosomal dominant inheritance and can show phenotype in the offspring [7]. *However, the developmental stage of mitochondria that are made up of OPA1 protein remains **unknown** [3].*

My **primary goal** is to learn about the developmental stage of mitochondria in the retinal ganglion cells that can be mutated by OPA1. I will use Danio rerio (zebrafish) as the model organism to conduct the experiments since the zebrafish have rapid and transparent embryonic development, which is beneficial for observation [8]. I **hypothesize** that the mutation of mitochondria could occur from the embryonic stage to the early childhood stage. My **long-term goal** is to further investigate the optic atrophy type 1 phenotype and find potential compounds that can rescue the symptoms.

Aim 1: Identify the developmental stage mitochondria in the retinal ganglion cells that are associated with optic nerves and OPA1.
Approach: I will use domain analysis on the zebrafish OPA1 gene sequence to determine the site that caused the mutation. Then I will use genome sequencing to determine the developmental stage of the gene. A few stages are determined for observation: embryonic stage, after hatching, first month, and every month until the sixth month. These two techniques would allow me to see what time the mutation will happen and will the mutation cause phenotype change in the zebrafish models.
Rationale: I can determine the mutation segment in the OPA1 gene and the developmental stage of optic atrophy type 1 in zebrafish models by analyzing the data collected.
Hypothesis: I hypothesize that the developmental stage of optic atrophy type 1 ranges from early embryonic stage to pre-production.

Aim 2: Identify compounds that can potentially rescue the phenotype of optic atrophy type 1.
Approach: I will use chemical screens on zebrafish models to identify if any compounds can rescue the disease-like phenotype. I will experiment on the embryonic stage of the zebrafish. By using chemical screens, I can determine the level of recovery of disease-like phenotype with each compound. I will select the same number of zebrafish for each compound, inject the same concentration of each compound, and monitor the phenotype in the same time frame.
Rationale: Chemical screens can help me visualize the mitochondria structure of zebrafish, and I can see how the mutation in the OPA1 gene leads to the change in structure. I can further determine which chemical compounds work the best in rescuing the disease-like phenotype and use in drug discovery.
Hypothesis: I hypothesize that different compounds rescue different phenotypes, and there are a few compounds that can rescue the phenotype and go onto drug discovery for the treatment of optic atrophy type 1.

Works Cited

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