***Specific Aims***

Gaucher disease (GD) is the most common lysosomal storage disease and is inherited in an autosomal recessive fashion [1]. GD can produce a broad range of symptoms affecting the blood, spleen, liver, bone marrow, and neurological function [2].  The disease is caused by the accumulation of glucocerebrosides, which are components of animal muscle and nervous tissues [3]. Glucocerebrosides are normally hydrolyzed in the lysosome by glucocerebrosidase (Gcase) [2]. GD is most commonly caused by mutations in the gene that encodes for Gcase, *GBA.* However, in a small number of patients, glucocerebroside accumulates due to a lack of saposin C (SapC), an essential activator of Gcase [4].  SapC is encoded by the *PSAP* gene, which will be the focus of this study.

Patients with the exact same homozygous *GBA* mutation can exhibit variability in the symptoms [5]. It has also been demonstrated that mice with mutations in both *GBA* and *PSAP* have more severe phenotypes than mice with only *GBA* mutations [6]. In humans, however, it is unknown how variations in *PSAP* influence the phenotypes of patients who already have GD. **Here we will test the hypothesis that variations in *PSAP* contribute to the phenotypic variability in GD patients with mutations in *GBA*.**

Our **Long-term goal** is to identify how variations in *PSAP* contribute to different phenotypes of GD patients.

We will pursue the following specific aims:

1. **Aim:** Identify *PSAP* variants that are associated with patients who have the same *GBA* mutation, but do not exhibit the same symptoms.

**Approach**: Sequence the *PSAP* and *GBA* gene for patients with GD. Identify differences in patients with the same mutation in the *GBA* locus, but with different phenotypes and *PSAP* sequences.

2. **Aim:** Examine the effects of overexpression of wild type *PSAP* in mice with the same *GBA* mutation.

**Approach**: Using CRISPR-Cas9, transgenic mice will be created that overexpress *PSAP* and have the same *GBA* mutation. The phenotypes of these mice will be compared to a control group of mice that do no overexpress *PSAP.*

3. **Aim:** Compare tissue specific levels of *PSAP* expression in GD patients.

**Approach**: Using SAGE, the level of *PSAP* mRNA will be measured in tissues that exhibited variability in symptoms of GD patients identified in aim one. The amount of expression will be compared to a control group of people without GD. This will help determine if the amount of PSAP expressed plays a factor in the variability of disease symptoms.

The discovery that *PSAP* plays a role in the symptoms of GD patients with the same *GBA* mutation would illuminate one of the mysteries of the disease. This may eventually lead to the clinical improvements via the development of therapies to modify PSAP levels in patients.

Sources Cited

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