

# A Drosophila model for studying mechanisms of Gauchers disease and synucleinopathies

<https://www.neurodegenerationresearch.eu/survey/a-drosophila-model-for-studying-mechanisms-of-gauchers-disease-and-synucleinopathies/>

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### Country

USA

## Title of project or programme

A Drosophila model for studying mechanisms of Gauchers disease and synucleinopathies

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NIH (NIA)

## Total sum awarded (Euro)

€ 1,502,701.83

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30/09/2015

## Total duration of award in years

2

## The project/programme is most relevant to:

Parkinson's disease & PD-related disorders|Motor neurone diseases|Neurodegenerative disease in general

## Keywords

glucosylceramidase, Gaucher Disease, synucleinopathy, Lewy Body Dementia, Glucosylceramides

## Research Abstract

? DESCRIPTION (provided by applicant): Gaucher's disease (GD), the most common lysosomal storage disorder, is caused by recessively inherited mutations in the glucosidase, beta, acid (GBA1) gene, which encodes glucocerebrosidase, a lysosomal enzyme that catalyzes the breakdown of the sphingolipid glucosylceramide. GD encompasses a wide spectrum of clinical symptoms, including severe and untreatable neurological abnormalities. Over the past ten years it has become increasingly clear that patients with GD also have a dramatically elevated risk of Parkinson's disease (PD), a common movement disorder characterized by the death of dopaminergic neurons in the midbrain and the accumulation of intracellular neuronal protein aggregates known as Lewy bodies. More recently, this finding has led to the discovery that heterozygous mutations in GBA1 are the most common genetic association with PD and Lewy body dementia (LBD), possibly accounting for 7-10% of these diseases. The mechanisms by which GBA1 mutations cause neurological symptoms of GD, and increase the risk of PD and LBD, are poorly understood. We hypothesize that the neurological symptoms of GD derive from the lysosomal accumulation of glucosylceramide, and a consequent defect in the degradative capacity of the lysosome. We further hypothesize that mutations in GBA1 increase the risk for PD and LBD by impairing the lysosomal degradation of  $\alpha$ -synuclein protein, a major component of the Lewy body aggregates that define both of these diseases. Finally, we hypothesize that genetic modifiers largely account for the poor genotype-phenotype correlation observed in GD and the low penetrance of GBA1 mutations in PD and LBD. To explore these hypotheses, we have created a Drosophila model of glucocerebrosidase deficiency that exhibits shortened lifespan, locomotor and memory deficits, neurodegeneration, and accumulation of protein aggregates. We propose to use our Drosophila model of glucocerebrosidase deficiency, as well as an existing mouse model of glucocerebrosidase deficiency, to pursue three aims. First, we will test the hypothesis that lysosomal glucosylceramide accumulation is responsible for the phenotypes of our Drosophila model of glucocerebrosidase deficiency. Second, we will test the hypothesis that glucocerebrosidase deficiency impairs lysosomal protein degradation, including the degradation of  $\alpha$ -synuclein. Third, we will conduct a genetic screen to identify novel modifiers of the phenotypes caused by glucocerebrosidase deficiency. Our work will contribute to a mechanistic understanding of GD, PD and LBD, and this insight will facilitate risk assessment in the clinic and provide a foundation for the development of treatments.

### **Lay Summary**

**PUBLIC HEALTH RELEVANCE:** Mutations in the glucosidase, beta, acid (GBA1) gene, which encodes glucocerebrosidase, cause Gaucher's disease, Parkinson's disease and Lewy body dementia. We have created a Drosophila model of glucocerebrosidase deficiency and propose to use this model to explore the mechanisms by which mutations in GBA1 cause these diseases. Our studies could facilitate risk assessment in the clinic, and also reveal targets for therapeutic intervention in these diseases.

### **Further information available at:**

#### **Types:**

Investments > €500k

#### **Member States:**

United States of America

#### **Diseases:**

Motor neurone diseases, Neurodegenerative disease in general, Parkinson's disease & PD-related

disorders

**Years:**

2016

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