Muscular Dystrophy on the Fly: A Proposed Role for *Drosophila* Gene *CG7845*

A project for Advanced Drosophila Genetics – BIOL 4110 - Stephanie Bergman, Shulamit Diena, Carla Murillo Perez and Talia Silver

Abstract

In this project, we use genetic modifier screens and protein data to predict the function of unknown *Drosophila* muscular dystrophy gene, *CG7845.* We propose that *CG7845* likely functions as a protein scaffold and histone reader, and stabilizes the functions of Dys and Dg, which are implicated in muscle dystrophy.

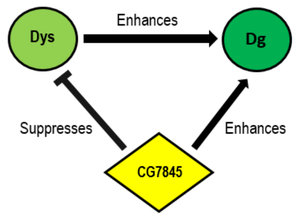
Introduction

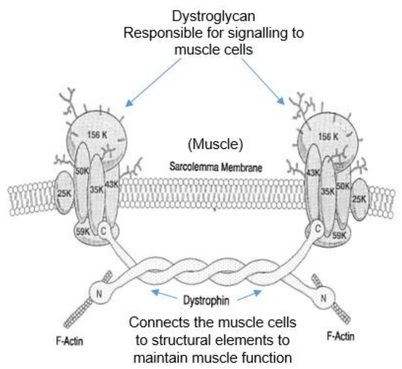
Who? *Drosophila melanogaster*, better known as the common fruit fly, is a powerful tool for human genetic disease research.

Why? Aside from being inexpensive and easy to breed, fruit flies share 75% of human genetic disease genes. This makes them ideal candidates for genetic research.

What? While the *Drosophila* genome is well studied and classified, the cellular function of many fly genes are yet unknown.

In this project, we investigate *CG7845,* a *Drosophila* gene implicated in Duchenne muscular dystrophy. It is known that *CG7845* interacts with Dystrophin and Dystroglycan – important components in skeletal muscle. However, its cellular function is unknown.





(Ervasti et al. 1991)

Research Methodology

Gene selection:

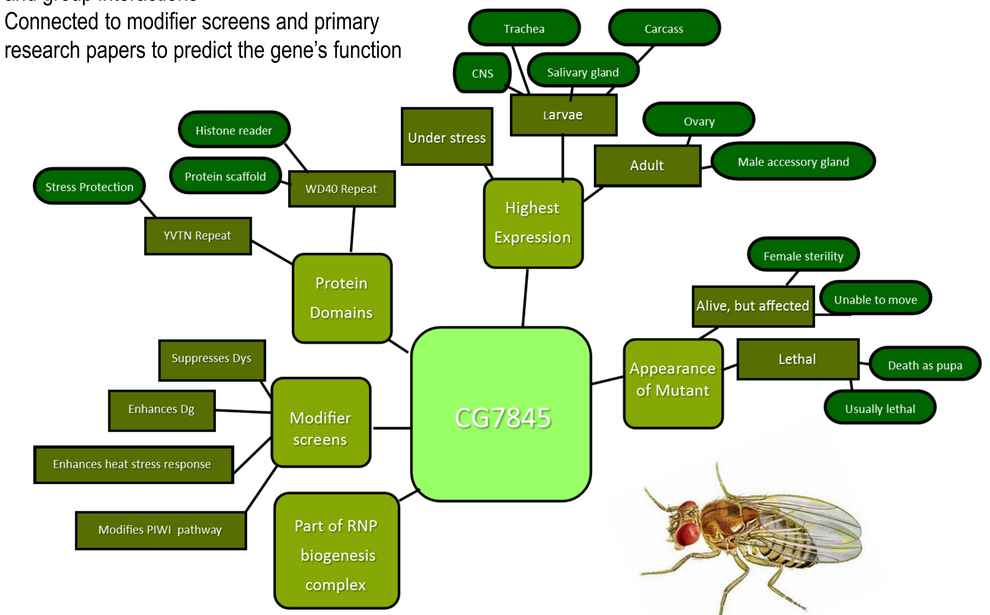
- Investigated molecular mechanism of DMD Located modifier screens for *Drosophila* DMD, and selected *CG7845,* gene of unknown function

Function prediction:

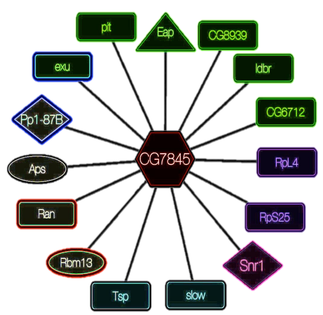
- Consulted *Drosophila* databases Flybase and DroID for *CG7845* interactions and characteristics
- Used Cystoscape bioinformatics software to map and group interactions
- Connected to modifier screens and primary research papers to predict the gene's function

Results

- *CG7845* highly expressed under stress, in reproductive areas, and various areas of the larva
- Modifies Dys, Dg, PIWI pathway and stress response
- Protein domains associated with histone readers, scaffolds and stress responders
- See flowchart for breakdown of results:



CG7845-interacting proteins largely include those involved in:

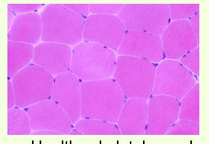


- Muscle cell homeostasis and locomotion (blue)
- Ribosome structural components (purple)
- Ribonucleoprotein biogenesis (green)
- Neurogenesis (yellow)
- Cell signaling (pink)
- Spindle assembly and elongation (red-lined)
- Ovary and sperm related processes (blue-lined)
- DNA binding (triangle)

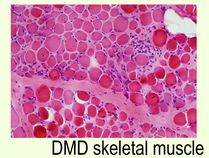
(Image generated using Cytoscape software)

About Duchenne Muscular Dystrophy (DMD):

- DMD is an X-linked genetic disorder found mainly in boys
- It is characterized by rapid muscle weakening, wasting and degeneration during childhood (National Human Genome Research Institute 2013).
- DMD is brought on by a dysfunctional Dystrophin-Dystroglycan complex, which connects muscle cells and the actin cytoskeleton. This complex is crucial for muscle signaling, stability and movement. Once the complex is damaged, it cannot be replaced. Note the change of shape in DMD muscles.



Healthy skeletal muscle (Seidman 2015)



DMD skeletal muscle (Neuromuscular.wustl.edu 2014)

Conclusions

- *CG7845* likely takes on a number of roles within the cell, including:

(1) Functioning as a histone reader:
- Activate transcriptions of genes involved in combatting heat and general stress responses in muscle cells, salivary gland, CNS and germ cells
- Regulating the transcription of miRNA (needed for proper muscle function)
- Read or regulate genes part of the PIWI pathway

(2) Functioning as a protein complex scaffold:
- Ribosomes and RNPs in muscle cells and the CNS can generate proteins for muscle activity and proper locomotion
- Facilitates the synthesis of piRNAs to protect germ cells from transposable elements
- Scaffold in the assembly of the spliceosome, which can successfully splice Dys mRNA

- These process are all important contributors to proper muscle function, and therefore flies lacking this gene would display poor muscle function and stress response, as well as worsened muscular dystrophy.

Naming the Gene:

- In classical *Drosophila* genetics, genes are named after their mutant form
- As such, we name *CG7845,* **"*Frosty,*"** because, like a snowman, the mutant fly is unable to move and cannot function in the heat

Fly picture: www.darwinmuseum.ru/expos/floor2/img/drozofila_b.jpg