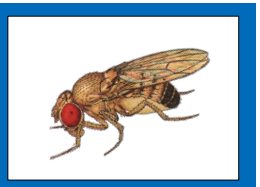
Metabolic Dysfunction in Frontotemporal Dementia

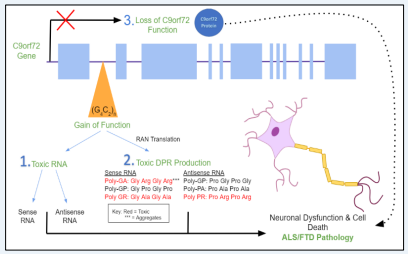
N. d'Almeida, K. Eby, A. Freeman, C. Gilmore, M. Salamone, and M. Tipping
Department of Biology, Providence College, Providence, RI 02918
email: mtipping@providence.edu



Abstract

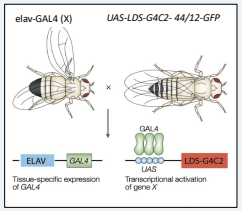
Frontotemporal dementia (FTD) is a neurodegenerative disease characterized by changes in behavior, a decline in executive function, and a loss of language abilities. With increased awareness that metabolic changes often present in disease, there has been a shift toward investigating the metabolic etiology of diseases, such as cancer. However, this shift is not as prevalent in the study of neurodegenerative disease. Using a Drosophila melanogaster model, we are studying the connection of neurodegeneration with the dysregulation of lipid metabolism associated with FTD. We utilized staining to visualize lipid stores and quantify brain volume, and metabolic assays to quantify oxygen consumption rate, extracellular acidification rate, and triglyceride levels. The goal of this project is to evaluate the dysregulation of lipid metabolism in FTD and determine targets for potential treatments.

FTD Background



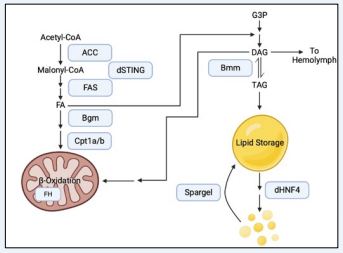
Harrington, 2020

GAL4-UAS Expression System

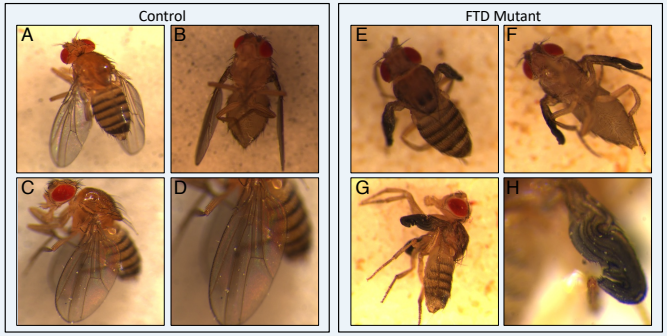


St Johnston, 2002

Lipid Metabolism



Phenotypic Changes in FTD Mutant Flies



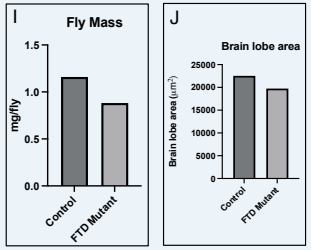


Figure 1:
A-D) Unfolded wings of control flies (*elav-GAL4; UAS-G4C2-12-GFP*) imaged from the top (A), bottom (B), and side (C, D).
E-H) Folded wings of FTD mutant flies (*elav-GAL4; UAS-G4C2-44-GFP*) imaged from the top (E), bottom (F), and side (G, H).
I) Mass of one fly averaged from weighing 15 flies.
J) Average area of one lobe from control and mutant fly brains.

Determining Volume of Fly Brains

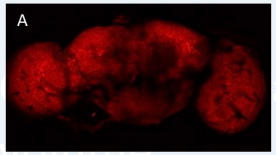
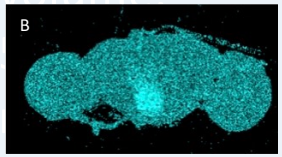


Figure 2:
A) Phalloidin stain of adult fly brain



B) 3D viewer image of fly brain shown in 2A for volume analysis in FIJI.

Calculated brain volume:
5.2×10^7 cubic microns

Measuring Metabolism in Fly Brains

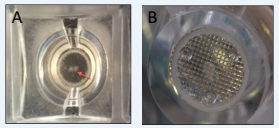
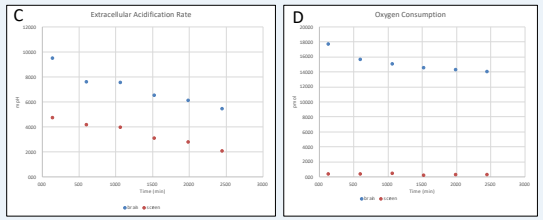


Figure 3:
A) Agilent Seahorse XF Analyzer cell plate well with brain.
B) Agilent Seahorse XF Analyzer cell plate well with brain and microtissue restraint.
C) Extracellular acidification rate (ECAR) in mpH/min
D) Oxygen Consumption Rate (OCR) in pmol/min



Lipid Storage in FTD Mutant Fat Bodies

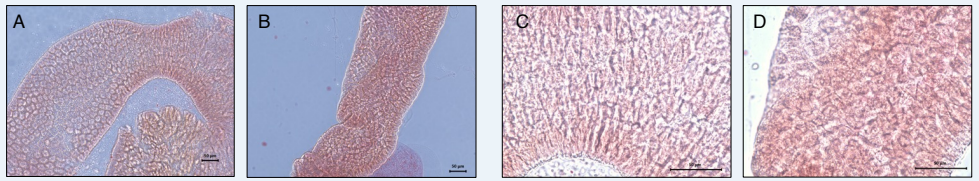


Figure 4: A-B) Oil Red O lipid stain of control (A) and FTD mutant (B) fat bodies at 20x magnification.

Figure 4: C-D) Oil Red O lipid stain of control (C) and FTD mutant (D) fat bodies at 60x magnification.

Metabolic Changes in FTD Mutant Flies

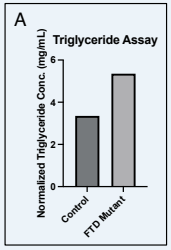


Figure 5:
A. Triglyceride concentration of 4 control and 4 mutant FTD flies measured in mg/mL, divided by protein concentration to account for size differences.

Conclusions

1. FTD mutant flies (*elav-GAL4; UAS-G4C2-44-GFP*) had folded wings, while control flies (*elav-GAL4; UAS-G4C2-12-GFP*) had unfolded wings (normal).
2. FTD mutant flies had less mass than control flies and smaller brain size (area).
3. Phalloidin staining allowed us to determine a control brain volume against which we can compare brain volume of FTD mutants
4. A baseline OCR and ECAR for control fly brain metabolism were established.
5. FTD mutant fly fat bodies showed greater Oil Red O lipid staining intensity than control flies.
6. FTD mutant flies had increased TAG levels.

Future Directions

1. Express the current driver at a restricted temperature until eclosion.
2. Investigate the expression of the FTD mutation only in the wing.
3. Repeat all assays to confirm results and observe significance.
4. Investigate brain metabolism using the established baseline.
5. Repeat phalloidin stain and collect more volume mesasuremnets.
6. Use caspase staining to investigate neuron death.

References

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Acknowledgements

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