Downregulation of GTP binding in APP mutation-related sporadic Alzheimer's disease

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Introduction
Alzheimer's Diseases is the sixth leading cause of death in the United States (about 500,000 deaths per year) and causes significant difficulty in the lives of 5 million patients and their families and caregivers. The causes and pathology of Alzheimer's are not well understood although apolipoprotein E (APOE) mutations have been shown to be significant, especially in women. Indicated in the mutation's pathology is its interactions with amyloid precursor protein (APP.) Wild-type APOE increases the degradation of amyloid protein while the e4 allele is less effective, leading to agglomeration of the protein into destructive plaques. While APP has no known function as a receptor, it has been shown to interact with GTP-binding protein G(o) and it is therefore suspected that improper APP-GTP binding is a factor in the development of Alzheimer's. Understanding the ultimate causes of Alzheimer's on a molecular level is essential in the development of potent treatments and cures.

Methods
I used publicly available dataset GSE4226 containing blood gene expression of 28 sporadic Alzheimer's and control patients. I used all samples and compared gene expression of sporadic and control individuals with a two-tailed student's t-test to isolate potential biomarker genes whose expression highly correlates to disease status. I used the hypergeometric test in the BiNGO plugin for Cytoscape to identify overrepresented molecular functions of upregulated and downregulated biomarkers. I then investigated the interactions and networks of indicated biomarkers using STRING.

Results
In analyzing data from control and sporadic Alzheimer's patients, 98 mRNAs were found to be downregulated in sporadic Alzheimer's patients with $p<.05$. Among downregulated genes, the molecular function of GTP binding was significant with $p<.05$. Downregulated biomarkers indicated in the GTP binding process were GTPBP1, RAB31, GNAI2, RAB5A, DRG1, and EIF2B2. GTP binding protein 1 (GTPBP1) and developmentally regulated GTP binding protein 1 (DRG1) bind GTP while EIF2B2 is significant in the GDP-GTP process. The other genes also play important roles in the formation of GTP-ligand complexes, including the GTP-APP complex.

Conclusion
This biomarker-selection method returned blood biomarkers for Alzheimer's disease indicating the significance of GTP binding in Alzheimer's pathogenesis while suggesting targets of treatments as well as minimally invasive detection of disease. Downregulation of the aforementioned GTP binding-related genes in the blood indicates disease state and can be detected through blood tests alone. This method also has implications in the development of treatments.

Keywords: mRNA expression, alzheimer's, GTP binding.

References:
1. Nishimoto, I.; Ogata, E.; et al. Nature, 1993, 362, 75-79.
2. Shahani, N.; Subramaniam, S.; et al. J Biol Chem, 2014, 289(9), 5799-808.

Marianne first learned about miRcore when she attended the 2012 Computational Biology Summer Camp. After the camp, she started the GIDAS chapter at Community High School with another student and has been a miRcore volunteer ever since. During the 2012-2013 school year, the CHS GIDAS Club raised over $2,000 for type 1 diabetes research and hosted a guest speaker from the University of Michigan. Marianne has won awards at the 2013 and 2014 MiRcore Genes and Health Contests.

Marianne is a science writer with Communicator, Community High School's student newspaper. She plays oboe in the Pioneer High School Symphony and Marching Bands and has been in the Michigan Youth Symphony Orchestra. She also enjoys playing chamber music with friends.

In March, Marianne spoke about personalized medicine and youth involvement in biomedical research at the 2014 TEDxYouth@AnnArbor event. She was one of 600 students selected as semifinalists in the 2014 USA Biology Olympiad. Marianne was also a finalist for the 2014 Ann Arbor News Young Citizen of the Year award and is a 2013-2014 Junior Rotarian.

She volunteered as a counselor in training at the Ann Arbor YMCA's Camp Al-Gon-Quian during the summer of 2013 and enjoys spending time with children, especially her wonderful younger sister, Allison. Marianne also enjoys running, cooking, gardening, and physics.

Although her future plans are uncertain, Marianne hopes to attend college for molecular biology and eventually pursue a career researching human diseases.