**Introduction**

- Alzheimer’s Disease is the most common form of dementia, and currently affects over 3 million people worldwide, and accounts for 60 – 80% of all dementia cases.
- Alzheimer’s comes in primarily two different forms – early-onset and late-onset. Early-onset Alzheimer’s occurs when a person is diagnosed with Alzheimer’s under the age of 65, and is caused by a mutation of Amyloid precursor protein, or APP. Late-onset Alzheimer’s occurs when a person is diagnosed after the age of 65, and is mainly caused by a mutation of the gene APOE, and specifically allele e4.
- When APP breaks down its proteins into simpler structures (known as proteolysis), it creates a substance known as beta-amyloid (abbreviated as Aβ) that forms plaques between nerve cells in the brain, thus believed to cause Alzheimer’s.
- APOE is a gene responsible for transporting lipids throughout the body. APOE4 (the e4 allele) increases the risk for Alzheimer’s, but does not guarantee it.
- A hallmark of Alzheimer’s is severe loss of memory which is associated with a deterioration of synaptic plasticity. Beta amyloid, the substance that characterizes Alzheimer’s, induces a microenvironment known as glial scars, causing it to be taken up by NMDA receptors. However, the overactivation/hyperactivity of these NMDA receptors leads to apoptosis, thus promoting Alzheimer’s disease.
- In Kanekiyo et al’s paper, “APOE and Alzheimer’s disease: accidental encounters or partners?”, they explore the relationship APOE and Alzheimer’s disease. The group found that one function of APOE is to regulate the amount of Aβ in the cell, and a mutation of APOE could affect these levels of Aβ, thus promoting Alzheimer’s Disease.
- In conclusion, the gene “GRIN2B” has a significant relation to Alzheimer’s and its candidate genes, APP/APOE4. More research should be conducted towards understanding how NMDA receptors like GRIN2B and it’s interaction with other Alzheimer’s related genes could affect the pathology of Alzheimer’s Disease and similar neurodegenerative disorders like Parkinson’s and Huntington’s disease.
- The top fifteen genes for each donor are depicted in the graphs above. These genes had average fold change values between 9 and 25. Note the y-axis scale for these graphs slightly differ from one another.

**Methods**

- Using the Allen Brain Atlas (http://www.brain-map.org), four of six donor brains were used for this research project (these donors are listed as H2551, 2001, H3551, 1000, H3551-1015, H3551-1012 but will be referred to as Donors 1-4 for the duration of this report). Because Alzheimer’s mainly affects the hippocampal region of the brain, a correlation analysis was done between the hippocampal and grey matter areas of the brain. Genes with a fold change greater than 3.0 in each of the four brains were collected so further research could be performed. The heatmap provided in Part 1 shows the distribution of genes in all four of the donor brains.
- Next, the gene expression data collected from the Allen Brain Atlas, were compared for common and unique genes in an online Venn Diagram generator (Venny: http://biothings.ncbi.nlm.nih.gov/tools/venn/). Once the common genes were collected, they were used for statistical analysis, while the top fifteen genes for each donor were graphed separately.
- To conduct the statistical analysis, Python was used to note the different statistical parameters and distribution frequencies for each of the four donors.
- The bioinformatics database DAVID (https://david.ncifcrf.gov/summary.jsp) was used for gene profiling based on Gene Ontology classification. The STRING database (https://string-db.org/) was used to construct protein interaction network for GRIN2B based on experimental evidence.

**Part 1: Gene Expression Profiling**

- The heatmap shows the distribution of genes in the four donors. A differential search was run that compared the hippocampal formation (HF) to the gray matter area (GM) of the brain. The genes are listed on the left side of the heatmap, and are ordered by the varying degrees of fold changes that exist in the correlation. A sample of these genes that had a fold change greater than 3.0 were used for subsequent analysis.

**Part 2: Common Genes**

- Using Venny, all of the genes from all four donor brains were collected and then plotted into the resulting Venn Diagram. Lists 1-4 represent Donors 1-4, respectively. There were 143 genes that were common between all four donor brains. These genes were later profiled using Gene Ontology annotation.

**Part 3: Graphing Common Genes**

- The top fifteen genes for each donor are depicted in the graphs above. These genes had average fold change values between 9 and 25. Note the y-axis scale for these graphs slightly differ from one another.

**Part 4: Statistical Analysis**

- Using a Python script, different statistical measures are given for the fold change data for all four donor brains. The max fold change values for each brain were all in the 15-20 range, while the minimum values were about 3 for all of them. The means range from 4.5 to 5.0. The histograms are right skewed. This indicates that there is a higher frequency of genes with a lower fold change compared to those with a higher fold change value. This histogram information can be found in the next column.

**Part 5: Gene Classification**

- Upon evaluating all of the genes through the DAVID database, GRIN2B was identified to be directly associated with Alzheimer’s disease. A protein – protein interaction network of GRIN2B also identified several genes associated with Alzheimer’s (CALM2, CAPN1, GRIN1, PARK2) and Huntington’s disease (GLI4, GRIN1, GRIN2B).

**Part 6: Conclusion**

- Through Zhang et al’s research paper, “Disruption of NMDA receptors in Alzheimer’s disease”, GRIN2B was discovered to be a type of NMDA receptor. NMDA receptors are types of glutamate receptors that are extremely important in synaptic plasticity. Beta amyloid, the substance that characterizes Alzheimer’s, induces a microenvironment known as glial scars, causing it to be taken up by NMDA receptors. However, the overactivation/hyperactivity of these NMDA receptors leads to apoptosis, thus promoting Alzheimer’s disease.
- In Kanekiyo et al’s paper, “APOE and Alzheimer’s disease: accidental encounters or partners?”, they explore the relationship APOE and Alzheimer’s disease. The group found that one function of APOE is to regulate the amount of Aβ in the cell, and a mutation of APOE could affect these levels of Aβ, thus promoting Alzheimer’s Disease.
- In conclusion, the gene “GRIN2B” has a significant relation to Alzheimer’s and its candidate genes, APP/APOE4. More research should be conducted towards understanding how NMDA receptors like GRIN2B and it’s interaction with other Alzheimer’s related genes could affect the pathology of Alzheimer’s Disease and similar neurodegenerative disorders like Parkinson’s and Huntington’s disease.
- In conclusion, by combining both the data collected from DAVID/STRING and the additional research, it is clear that there are innate relationships between both early- and late-onset Alzheimer’s, and both are impacted by a variety of different factors, notably NMDA receptors such as GRIN2B. By researching these NMDA receptors, there will be a better understanding in the pathology of how Alzheimer’s Disease impacts the human mind.

**Gene Correlation Study of Early-Onset and Late-Onset Alzheimer’s Disease**

Avinash Singh, Northview High School, Sylvania, OH 43560 & BioScience Project, Wakefield, MA 01880