Transcriptional Changes of Genes Linked to Alzheimer's Disease

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Keywords: Alzheimer's Disease, GWAS, Bulk RNA-Seq.

Abstract: Alzheimer's disease is a pogressive neurodegenerative disease that constitutes most cases of dementia. This study aims to converge existing data from GWAS studies and bulk RNA-Seq from patients with and without Alzheimer's disease to prioritize genes involved in the disease pathology. For this study, I examine existing bulk RNA-Seq datasets from patients with and without Alzheimer's disease [GSE159699], focusing on genes previously identified as links to late-onset Alzheimer's disease in GWAS studies. I confirmed my results with a publicly available AD transcriptomics consensus tool published by the Swarup lab. In my analysis, I identified shared gene expression differences in STAG3L5P, MEF2C, MS4A6A, PILRA and CASS4 between Alzheimer's disease and control patients across several datasets. These genes were previously linked to late-onset Alzheimer's disease. Further investigation should explore how their mutations and gene expression differences contribute to the mechanisms underlying Alzheimer's disease.

1 INTRODUCTION

Alzheimer's disease (AD) was first diagnosed by Alois Alzheimers in 1907 in a case of a 51-year-old woman who was experiencing a relatively rapidly deteriorating memory along with psychiatric disturbances. Over time, the definition of AD has changed, and today we consider it to be a neurological disorder accompanied by a hallmark pathology: presence of extracellular amyloid beta plaques and intracellular neurofibrillary tangles formed of tau protein in the brain (Matthews, Xu, Gaglioti, Holt, Croft, Mack, McGuire. 2019); (Morgan, 2011). Currently, AD affects more than 20 million people worldwide, with about 135 million people expected to develop it by 2050 (Castellani, Rolston, Smith. 2010); (Fratiglioni, Ronchi, Agüero-Torres. 1999).

AD can be classified into two categories, early and late-onset, defined by the age of diagnosis and inheritance pattern (Masters, Bateman, Blennow, Rowe, Sperling, Cummings. 2015). Whilst early-onset AD forms around 10% of the cases, around 90% of AD cases are late-onset, with 85% of the patients older than 75 years of age (Rabinovici. 2019).

Multiple genetic mutations are responsible for the development of AD. Mutations in genes processing amyloid beta proteins are linked to early-onset AD: APP, PSEN1 and PSEN2 (Masters, Bateman, Blennow, Rowe, Sperling, Cummings. 2015). Genome-wide association studies (GWAS) have identified a number of risk factors related to late-onset AD, including the APOE allele e4 (Rabinovici. 2019). APOE e4 carriers have a higher risk of developing late-onset AD, in contrast to carriers of e2 or e3 alleles. Subsequent GWAS studies have identified dozens other loci conferring risk factors for late-onset AD, including TREM2, ADAM10, ADAMTS1 and others (Kunkle, 2019); (Jansen, 2019).

To understand more about the mechanism behind the pathology of AD, I evaluated the expressions of genes linked to late-onset AD in patients with and without Alzheimer's disease. I assessed whether the genes that confer a known risk towards late-onset Alzheimer's disease are also differentially expressed in patients with Alzheimer's disease, regardless of their mutation status.

2 METHODOLOGY

Publicly available bulk RNA-Seq datasets from post-mortem temporal lobes from patients with and without Alzheimer's disease were used to investigate

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He, W.
Transcriptional Changes of Genes Linked to Alzheimer's Disease.
DOI: 10.5220/0011378300003443
In *Proceedings of the 4th International Conference on Biomedical Engineering and Bioinformatics (ICBEB 2022)*, pages 1112-1118
ISBN: 978-989-758-595-1

the expression of genes previously identified as linked to late-onset AD [GSE159699, 9]. The data was re-analyzed using DESeq2 in Rstudio (Michael, 2014). Six patients that were identified as outliers via PCA were removed from the dataset, including three patients with AD and three healthy controls. Using boxplots, I investigated the expression of genes previously identified as linked to late-onset AD (Kunkle, 2019); (Jansen, 2019) in the GSE159699 dataset. To compare my results with previously published literature, I investigated the expression of the genes linked to late-onset AD via a publicly available AD consensus transcriptomics resource developed by the Swarup lab (Morabito, 2020) which reanalyzed human AD gene-expression datasets from several resources, including the ROSMAP dataset (Bennett, 2018) and the Mayo dataset (Allen, 2016).

The main goal of this study was to investigate the expression of genes previously identified as associated with late-onset AD in GWAS studies, in bulk RNA-Seq data from post-mortem brains with and without Alzheimer's disease. For this, I identified genes of interest associated with late-onset AD published in recent GWAS studies (Kunkle, 2019); (Jansen, 2019). Using bulk RNA-Seq dataset from the temporal lobes of these patients, I compared the expression of the genes linked to late-onset AD in the temporal lobes of patients with and without AD [GSE159699, 9]. To relate my research to previously published literature, I compared my results to the AD consensus transcriptomics resources by the Swarup lab (Nativio, 2020) which was used to display AD consensus gene expression from multiple sources (Bennett, 2018); (Allen, 2016).

The GSE159699 dataset is a bulk RNA-Seq dataset from the temporal lobes of 12 patients with AD, 10 healthy age-matched controls to the AD patients and 8 healthy young controls (Nativio, 2020). First, I plotted all patients using a PCA plot and a heatmap of the top 20 differentially expressed genes in DESeq2 (Michael, 2014). I identified 6 outliers, that were significantly different from all the other patients. After removing the outliers from the dataset, the AD patients (n=9) were separated from the healthy young (n=4) and healthy old controls (n=7) in the PCA plot, with PC1 explaining 19% variance in the dataset (Figure 1). A heatmap of the top 20 differentially expressed genes did not identify any significant difference between AD patients and the healthy and young controls. This result was unremarkable and in line with previous results published by Nativio et al. (2020), who reported differences in expression among the genes related to epigenetic alterations (Nativio, 2020). The original paper by Nativio et al. (2020) analyzed gene expression of only genes related to the GO term 'regulation of transcription' (Nativio, 2020), whereas my heatmap graph presented the top 20 genes that were differentially expressed among the AD, young and old healthy controls (Figure 1).

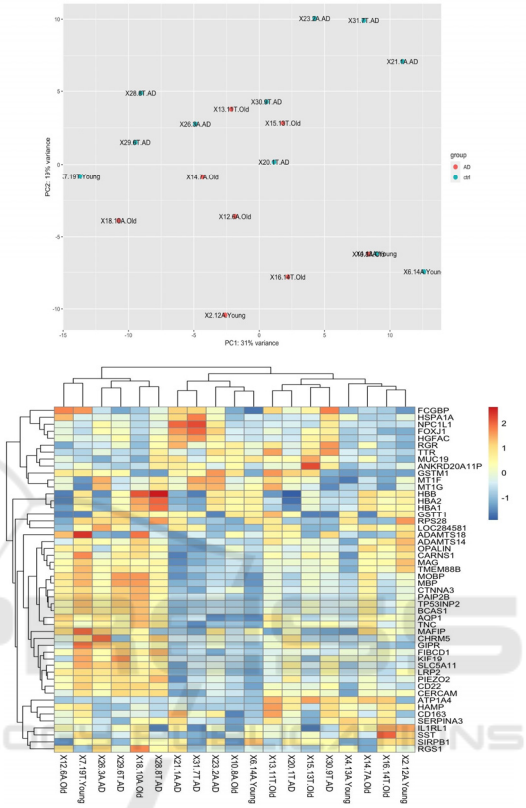


Figure 1: PCA and heatmap of top 20 differentially expressed genes among the bulk RNA-Seq data from the temporal lobes of patients with and without AD [GSE159699, 9].

Because genes that are differently expressed between AD and controls were previously discussed and reported in the original paper by Nativio et al. (Nativio, 2020), I did not seek to replicate the analysis, but instead decided to look into whether genes previously identified as links to late-onset AD in GWAS studies are differently expressed between AD and controls in the GSE159699 bulk RNA-Seq dataset which contained AD patients, along with old and healthy controls. For this, I identified genes linked to late-onset AD using previously published GWAS studies (Kunkle, 2019); (Jansen, 2019). For each gene previously identified as linked to late-onset AD, I reported whether it was differently expressed in the current dataset. In addition, I crossed my results with the AD transcriptomics consensus resource

developed by the Swarup lab (Morabito, 2020). This resource allows plotting of gene expression differences among the brains of AD patients, age-matched patients, and healthy controls. The plots below summarize fold-change expressions between AD and controls using the GSE159699 dataset (Nativio, 2020), and the AD consensus resource by the Swarup lab (Morabito, 2020).

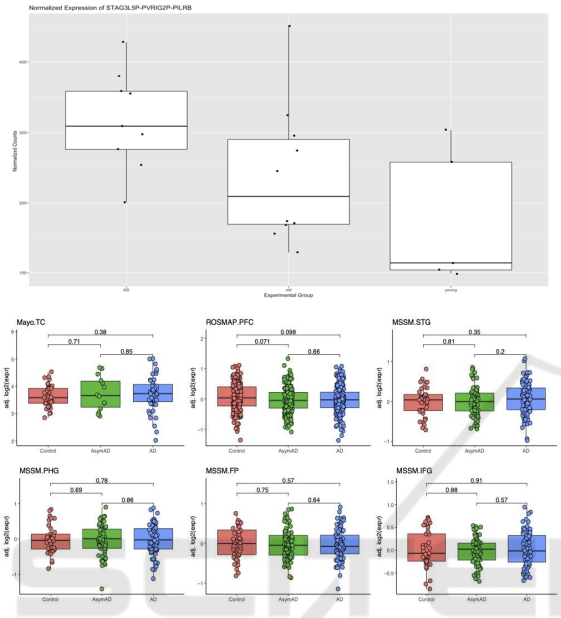


Figure 2: The boxplot of differences in STAG3L5P-PVRIG2P-PIL gene expression among AD, along with healthy young and old controls indicates a significant increase of expression of STAG3L5P - PVRIG2P - PIL in the AD group. On the left is the boxplot of gene expression differences plotted using the bulk RNA-Seq data from the temporal lobes of patients with and without AD [GSE159699, 9]. On the right is the boxplot of gene expression differences in bulk RNA-Seq datasets using the AD gene expression consensus resource developed by the Swarup lab (Morabito, 2020). Three published datasets show an upregulated expression while three shows a downregulated expression.

The STAG3L5P gene displays an increase in expression in AD vs control patients in the GSE159699 dataset. When compared to the AD consensus transcriptomics resource by the Swarup lab, STAG3L5P also showed an increase in expression in the ROSMAP dataset (Fig.7a). Previously, the exome-sequencing studies showed that the associations with two variants in a novel gene STAG3 were also replicated and significantly associated with AD in the replication analysis. The rare variants in STAG3 identified by WGS suggested the possibility that STAG3 has a distinct mechanistic role in AD which is different from other normal variants (Joshua, 2020).

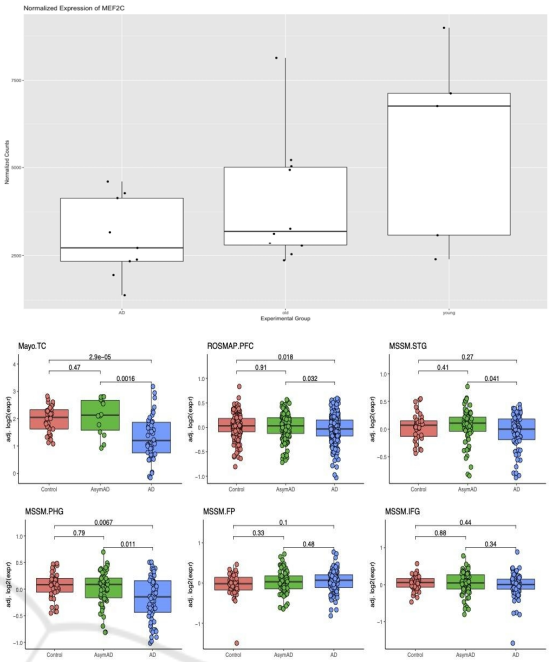


Figure 3: The boxplot of differences in ME2FC gene expression among AD patients, along with healthy young and old controls indicates a significant decrease in ME2FC of expression in the AD group. On the left is the boxplot of gene expression differences plotted using the bulk RNA-Seq data from the temporal lobes of patients with and without AD [GSE159699, 9]. On the right is the boxplot of gene expression differences in bulk RNA-Seq datasets using the AD gene expression consensus resource developed by the Swarup lab (Morabito, 2020).

A Similar process was performed for the MEF2C gene, which showed a decrease in expression in AD vs control patients in the GSE159699 dataset. Comparison to the AD consensus resource by the Swarup lab revealed unclear changes in gene expression between AD patients and the controls, displaying a decreased expression in AD brains using the Mayo and the MSMM dataset, but not in the other datasets (Figure 3). MEF2C has a role in conferring resilience to pro-inflammatory stimuli in microglia (Deczkowska, 2017). Microglia plays an important role in AD, and MEF2C restricts the microbial response to immune stimuli. Additionally, other GWAS studies show that mutations in MEF2C are linked to late-onset AD. Inflammation is known to be associated withcognitive dysfunction and may contribute to the pro-inflammatory milieu of the brain in AD or aging patients (Simen, 2011).

MS4A6A displays an increased expression in the AD group using the GSE159699 dataset, Mayo and MSSM dataset, but the gene expression relationship is unclear using the other datasets from the AD consensus resource by the Swarup lab (Nativio, 2020) (Morabito, 2020). Previous studies show that MS4A6A is associated with AD and is likely to have an immune-related function (Reitz. 2015); (Paul, 2011).

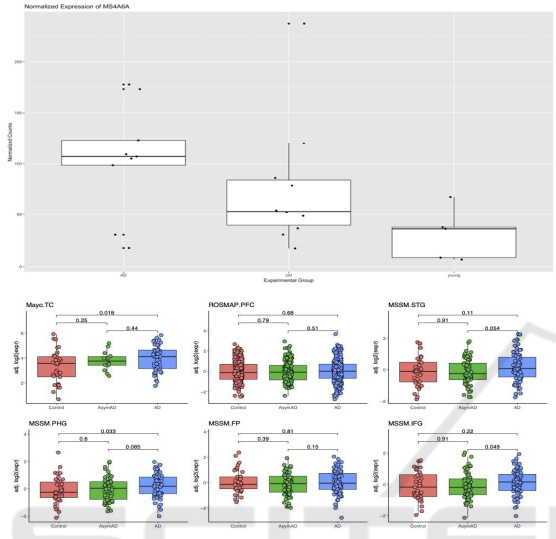
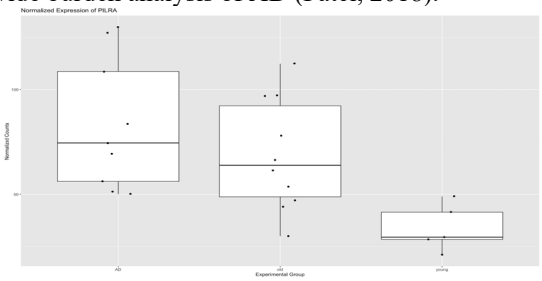


Figure 4: The boxplot of differences in MS4A6A gene expression among AD patients along with healthy young and old controls indicates an increase in MS4A6A of expression in the AD group. On the left is the boxplot of gene expression differences plotted using the bulk RNA-Seq data from the temporal lobes of patients with and without AD [GSE159699, 9]. On the right is the boxplot of gene expression differences in bulk RNA-Seq datasets using the AD gene expression consensus resource developed by the Swarup lab (Morabito, 2020).

The PILRA gene is associated with late-onset AD and exhibits an increase in gene expression in the AD vs control group in the GSE159699 dataset and the MSSM datasets from the AD consensus resource by the Swarup lab. Previous research revealed a significant burden of PILRA variants in the exome-wide burden analysis of AD (Patel, 2018).



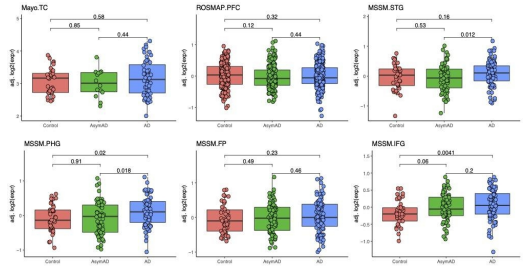


Figure 5: The boxplot of differences in PILRA gene expression among AD patients along with healthy young and old controls indicates an increase in PILRA expression in the AD group. On the left is the boxplot of gene expression differences plotted using the bulk RNA-Seq data from the temporal lobes of patients with and without AD [GSE159699, 9]. On the right is the boxplot of gene expression differences in bulk RNA-Seq datasets using the AD gene expression consensus resource developed by the Swarup lab (Morabito, 2020).

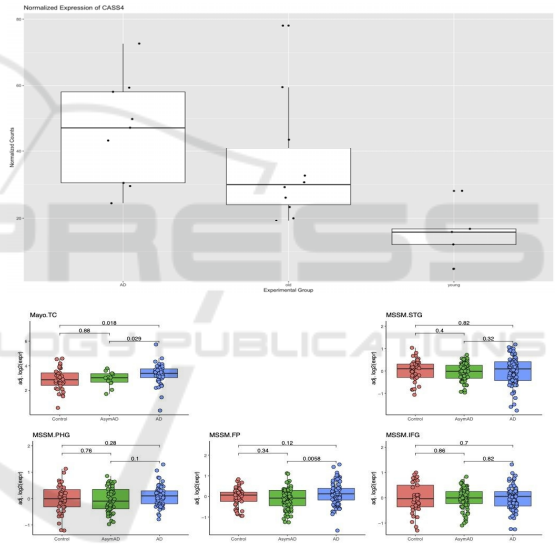


Figure 6: The boxplot of differences in CASS4 gene expression among AD patients along with healthy young and old controls indicates an increase in CASS4 expression in the AD group. On the left is the boxplot of gene expression differences plotted using the bulk RNA-Seq data from the temporal lobes of patients with and without AD [GSE159699, 9]. On the right is the boxplot of gene expression differences in bulk RNA-Seq datasets using the AD gene expression consensus resource developed by the Swarup lab (Morabito, 2020).

The CASS4 gene exhibits an increase in expression in AD patients vs the control group in the GSE159699 dataset as well as the Mayo dataset using the AD consensus resource from the Swarup lab. CASS4 was previously found to be associated with the amyloid, tau pathology, cytoskeletal function and

the axonal transport pathways identified in GWAS studies (Reitz. 2015). It was found to retain the motifs required for the interaction with PTK2B and to contribute to the pathology of AD (Beck, 2014).

3 DISCUSSIONS

AD is a progressive neurodegenerative disease that accounts for the most cases of dementia. This study aimed to converge existing data from GWAS studies and RNA-Seq to prioritize the high-risk genes for AD. I found that 5 genes, STAG3L5P, MEF2C, MS4A6A, PILRA and CASS4, were both linked to AD in the GWAS studies and differentially expressed in the RNA-Seq analysis between the AD and control groups using the GSE159699 dataset (Nativio, 2020). To validate my findings, I compared my results with an AD transcriptomics consensus tool published by the Swarup lab (Morabito, 2020), that reanalyzed golden-standard bulk RNA-Seq datasets from AD patients along with healthy old and young controls using various datasets, including Mayo and ROSMAP (Bennett, 2018); (Allen, 2016).

4 CONCLUSIONS

My analysis shows that STAG3L5P, MEF2C, MS4A6A, PILRA and CASS4 exhibit changes in expression between AD and control patients that are fairly consistent across different datasets. These results suggest that these genes could be particularly important in AD. All these genes were previously found to be associated with AD in GWAS studies (Kunkle, 2019); (Jansen, 2019). In addition, their gene functions are relevant to AD mechanisms. STAG3LAP has several rare variants identified through exome-wide analysis, with suspected distinct mechanisms in causing AD (Joshua, 2020). MS4A6A has a gene function associated with microglial function and immunity (Reitz. 2015); (Hollingworth, 2011). The five genes explored in this study should be further investigated to confirm their causality to AD, and the role of the genetic variants and changes in the expression of mechanisms leading to AD.

Further understanding of how STAG3L5P, MEF2C, MS4A6A, PILRA and CASS4 contribute to AD may be used for early detection, prevention and drug development in AD.

ACKNOWLEDGEMENTS

If any, should be placed before the references section without numbering.

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