EPISTASIS OF ALZHEIMER’S DISEASE

Abstract

Alzheimer’s disease (AD) is the most common form of dementia and it affects more than 50 million people worldwide. There have been decades of research work done in Alzheimer’s disease, but there is yet to be drugs that can slow the progress of this disease, let alone offer a cure. There are researches on the epistasis (gene – gene interaction) of Alzheimer’s disease but such studies are limited. To gain greater insight into the interactions of genes that increase or reduce the risk of Alzheimer’s disease in people, I propose to evaluate previously reported instances of epistasis in Alzheimer’s disease in a new larger dataset. My aim is to do a meta-analysis of genes that have been identified to be associated with Alzheimer’s disease and prioritize those that show the most promising interactions. These findings will advance our understanding of the role of epistasis in Alzheimer’s disease and I hope that the results may provide insights to the advancement of researches in progress to find drugs and cure for the disease.

Background

The study of epistasis in Alzheimer’s disease is an ongoing research that has proved worthwhile in identifying new gene interactions that are associated with Alzheimer’s disease. Although, not at its end stage, these studies are yielding promising results in the advancement of AD research. In 2009, Combarros et al. identified four interactions that have been consistently replicated, APOE4: ACT – 17AA; BACE1 exon5 GG; IL6 – 174C; BCHE K. Among these, BACE1 exon5 GG and APOE4 were discovered to be most significant in their interaction to increase AD risk. The effects of these genes were first analyzed using the locus-by-locus approach, but the main effects were so small that they could have been missed if epistasis was not used. In 2018, Gusareva et al. found a statistical epistasis signal between the SNPs rs3733980 and rs7175766 that was associated with Alzheimer’s disease in males. They found a convincing significance in the pair rs1477307 and rs4077746. These genes were identified to co-express in the temporal cortex brain of Alzheimer’s disease patients. Another study conducted by Robson et al. saw that the combination of TFC2 and HFEC282Y may lead to an excess of redox-active iron which induces oxidative stress in neurons. This stress is exacerbated in carriers of APOE4. They also

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identified that these two variants were associated with an increased risk of Alzheimer’s disease only in the presence of the other.\textsuperscript{4}

Most phenotypes are affected by multiple genes. The study of epistasis in Alzheimer’s disease can be used to identify genes that synergize to increase or decrease the risk for Alzheimer’s disease. It can point towards new Alzheimer’s disease related pathways and provide clues towards novel medical targets for the cure of AD.\textsuperscript{3} The study of epistasis in AD can enhance current research and open new research pathways and directions. Epistasis is a crucial feature of a complex disease like Alzheimer’s disease and more studies are needed to establish interactions.\textsuperscript{2}

Research Plan

With a new, larger dataset we recently developed, I propose to study epistasis in AD in this dataset using statistical methods. I will conduct an extensive and careful literature review of epistasis study and other experimental studies in AD. I will identify all the SNPs that have been previously found to be associated with AD both in the epistasis and other experimental studies. I will prioritize the promising interactions I find in my study and research more about the genes so that I can gain a better understanding of their interactions. I will do this by using gene databases like AlzGene to increase my biological understanding of epistasis. This will in turn enhance my statistical analyses of those genes.

Samples: Our dataset includes 38,876 subjects. There are 1,291,057,196 SNPs available in this dataset.

Candidate epistatic interactions:

TF – HFE: The transferrin gene (TF) is an iron-binding blood plasma glycoprotein that complexes iron, transports it in circulation and controls the level of free iron in biological fluids.\textsuperscript{5} The hemochromatosis gene (HFE) allows the body absorb iron from the diet.\textsuperscript{6} The epistatic interaction between rs1049296 (P589S) in TF and rs1800562 (C282Y) in HFE result in significant association with risk for AD.

CLU – MS4A4E: Clusterin (CLU) is a molecular chaperone that prevents unfolded secretory protein aggregation. Membrane spanning 4-domains A4E (MS4A4E) is a protein coding gene. The result of the interaction between rs1136000 – rs670139 (CLU – MS4A4E) shows a significant increase in the risk for Alzheimer’s disease.

I will add other SNP interaction as part of the study.

Statistical Analyses: I will analyze the data in R. The model of the analysis will be

AD status = SNP1 + SNP2 + age + sex + PC1-10 + (SNP1*SNP2).

Note: PC is the principal component of ethnicity and years. The age and sex will be PC included in the model will be adjusting for confounding so that the results of the study can be generalizable.

Limitations:

Statistical epistasis is not equal to real biological interactions so, findings will require careful follow-up. Epistasis is notoriously challenging to analyze because when counts are combined, the power (the probability that the test rejects the null hypothesis when the alternative hypothesis is true) of the result is difficult to retain.

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