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Analysis of APOE Variants in Onset of Alzheimer's Disease

Elaine Vanterpool
Oakwood University, evanterpool@oakwood.edu

Madison Burnett
Oakwood University

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Madison Burnett and Elaine Vanterpool, PhD
Oakwood University
Department of Biological Sciences
Huntsville AL, 35896

ABSTRACT

Alzheimer's disease is a disease characterized by memory loss and cognitive decline. This is the most common form of dementia. Alzheimer's is the 5th leading cause of death in humans, as it currently has no cure. Individuals who carry the APOE (Apolipoprotein E) gene, specifically APOE 4, have an increased risk of developing late-onset Alzheimer's disease. The purpose of this study is to analyze specific mutations in the APOE gene to determine if they may contribute to the onset of Alzheimer's disease. A web server database called Simple Clinvar was used to acquire information and statistics concerning Alzheimer's disease and the different genetic variants associated with the disease. The SIFT algorithm was used to predict whether the changes in amino acid sequences of the APOE gene were deleterious. PolyPhen was another prediction algorithm used to predict the influence that amino acid substitutions have on the expression and function of proteins. Apolipoprotein E (APOE) regulates lipid transport between cells and tissues in the body. APOE belongs to the Apolipoprotein superfamily, which consists of Apolipoprotein A-I, Apolipoprotein A-IV, and Apolipoprotein E. The conserved domains occur on the 1-176 interval. The Arg154Ser mutation was predicted to be probably damaging with a PolyPhen score of 0.850/1.0. The Arg152Gln mutation was predicted to be benign, with a PolyPhen score of 0.452/1.0. The substitution from Arg to Ser at position 154 is predicted to affect protein function with a score of 0.02. The substitution from Arg to Gln at position 152 is predicted to be tolerated with a score of 0.54. APOE is associated with multiple conditions in addition to Alzheimer's disease, such as age-related muscular degeneration 1, familial type 3 hyperlipoproteinemia, lipoprotein glomerulopathy, major depressive disorder, and sea-blue histiocyte syndrome. The expression of the mutations is found to be correlated with an increased risk of developing Alzheimer's disease.

INTRODUCTION

There are multiple factors that contribute to the onset of Alzheimer's disease. These include genetic causes, environmental factors, and lifestyle choices. Apolipoprotein E (APOE) is a gene that is associated with the onset of Alzheimer's disease. There are 3 main alleles of the APOE gene: apolipoprotein E 3 (APOE 3), apolipoprotein E 2 (APOE 2), and apolipoprotein E 4 (APOE 4). Expression of APOE 2 corresponds to a decreased risk of Alzheimer's disease, but it is associated with cardiovascular hemorrhages and complications. APOE 3 is the most common APOE allele, and it neither increases nor decreases the risk of Alzheimer's disease. APOE 4 has the highest risk factor for the onset of Alzheimer's disease. Individuals with two copies of the APOE 4 allele have a greater chance of developing Alzheimer's disease. This condition is characterized by progressive memory loss due to the death of neurons and a decline in brain health. Evidence suggests that there is a higher risk of developing AD when there is an interaction between APOE and amyloid beta peptide (Aβ). APOE degrades amyloid β to form amyloid plaques, which directly increases the pathogenesis of Alzheimer's disease. The aim of this study is to gain insight into the effect that variants of the APOE gene have on the onset of Alzheimer's disease.

METHODS

- Simple Clinvar was used to identify APOE as a gene associated with AD. This program also highlighted the various missense mutations that corresponded to APOE.
- SIFT (Sorting Intolerant From Tolerant) algorithm used to predict the outcome of amino acid substitutions on the function of proteins encoded by the APOE gene.
- PolyPhen was used to predict the severity of gene variations associated with APOE.
- A 3D-model was created using SWISS Model to display the mutations of the APOE gene.

RESULTS

PolyPhen-2

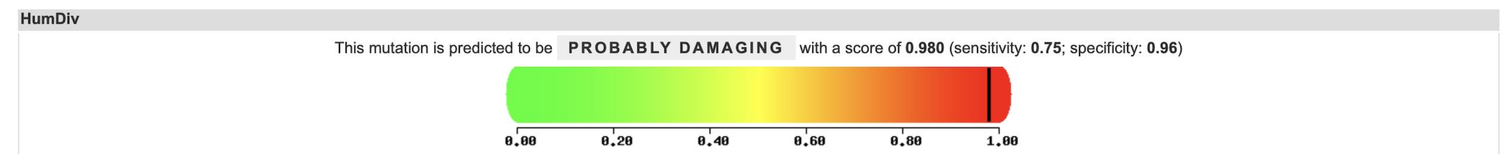

Figure 1(a). PolyPhen prediction for variant Arg to Ser at position 154.

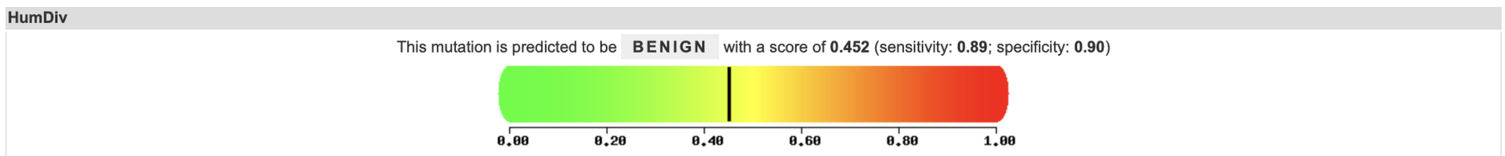

Figure 1(b). PolyPhen prediction for variant Arg to Gln at position 152.

SIFT

```
Substitution at pos 154 from R to S is predicted to AFFECT PROTEIN FUNCTION with a score of 0.02.
    Median sequence conservation: 3.75
    Sequences represented at this position:11
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Figure 2(a). SIFT prediction that Arg154Ser has an effect on protein function with a score of 0.02.

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Substitution at pos 152 from R to Q is predicted to be TOLERATED with a score of 0.54.
    Median sequence conservation: 3.75
    Sequences represented at this position:11
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Figure 2(b). SIFT prediction that Arg152Gln has a tolerated effect on protein function with a score of 0.54.

SWISS Model

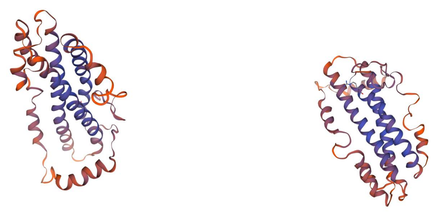

Figure 3. 3D configuration of the protein encoded by the apolipoprotein E (APOE) gene.

Conserved Domains

Figure 4 (a). APOE belongs to the Apolipoprotein superfamily which is associated with lipid transport.

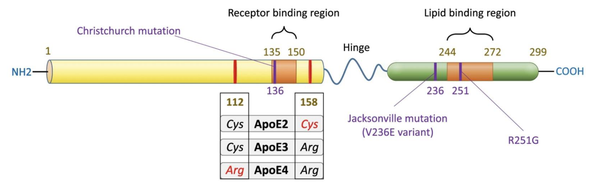

Figure 4 (b). APOE has an N-terminal domain containing the receptor binding region and a C-terminal region containing the lipid-binding region.

DISCUSSION AND CONCLUSION

This study observed that the expression of apolipoprotein E gene mutations can affect protein function and ultimately increase the risk of developing Alzheimer's disease. The Arg154Ser mutation was found to be potentially damaging and thus have an altering effect on protein function. A change in protein function can be damaging to an organism because it can alter cellular processes and overall capabilities. Mutated isoforms of APOE can bind stronger to amyloid beta peptide. This increases the likelihood of amyloid plaque formation from the deposition of amyloid beta. The accumulation of amyloid plaques can interrupt the synapses in the brain, which prevents cell signaling vital to carrying out cellular processes. Future studies could potentially focus on targeting the APOE-amyloid beta interaction to prevent the formation of amyloid plaques. The findings from this study could be used to help the medical community possibly find a way to limit the effects of Alzheimer's disease by maintaining the synapses of neurons in the brain.

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