# Computerized Medical Diagnosis Application using Protein-Protein Interaction Analysis for Alzheimer's Disease

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**Abstract:** *We have developed a computer programming application for Medical diagnosis for detection of Alzheimer's disease using analysis of oxidative proteins. Alzheimer's disease (AD) is a progressive, irreversible, and most common cause of dementia. Oxidative stress plays a significant role in the pathogenesis of Alzheimer's disease (AD), which is devastating and occurs in the elderly. The brain is more vulnerable than other organs to oxidative stress, and most of the components of neurons, such as lipids, proteins, and nucleic acids can be oxidized in AD due to mitochondrial dysfunction, increased metal levels, inflammation, and β-amyloid (Aβ) peptides. Oxidative stress participates in the development of AD by promoting Aβ deposition, tau hyperphosphorylation, and the subsequent loss of synapses and neurons. The relationship between oxidative stress and AD suggests that oxidative stress is an essential part of the pathological process, and antioxidants may be useful for AD treatment. It is common to use computational techniques, especially protein-protein interaction analysis, to mine the association between oxidative protein interaction networks and discover some regulation elements that are essential to the expression of proteins. The results of the study will be helpful in drug discovery and testing of particular disease requires preclinical and clinical trials.*

**Keywords:** Drug Discovery, Medical Diagnosis, Protein-Protein Analysis, Oxidative stress analysis, Alzheimer's disease

## 1. Introduction

Alzheimer's disease (AD) is a progressive, incurable neuro-degenerative disorder. Multiple processes have been implicated in AD, notably including abnormal β-amyloid (Aβ) production [1–7], tau hyperphosphorylation and neurofibrillary tangles (NFTs) (8, 9), synaptic pathology (10–12), oxidative stress [13–15], inflammation [5, 16–19], protein processing or misfolding [20, 21], calcium dyshomeostasis [15, 20–26], aberrant reentry of neurons into the cell cycle [27, 28], cholesterol synthesis [29, 30], and effects of hormones [23, 31] or growth factors [17, 32]. Nevertheless, the pathogenic factors that initiate these processes remain elusive.

As of year 2017, there were an estimated 50+ million people with dementia worldwide. This number will increase to an estimated 75.6 million in 2030, and 135.5 million in 2050. Much of the increase will be in developing countries. Already, 62% of people with dementia live in developing countries, but by 2050 this will rise to 71%. The fastest growth in the elderly population is taking place in China, India, and their South Asian and Western Pacific neighbors (http://www.alz.co.uk/research/statistics).

The results of several surveys have suggested that high levels of oxidative stress and free radicals, or decreases in the antioxidant and/or free-radical-scavenging capacity play a role in the development of neurodegenerative diseases [33]. In AD, oxidative stress is manifested in, for example, increased protein oxidation, lipid peroxidation, and formation of reactive oxygen species (ROS)[34]. In the presence of oxidative stress, proteins may modify their structure and function by cross-linking with other proteins, or through nitration or carbonylation, which generally leads to loss of function. Moreover, it is possible that the sporadic form of AD is initiated by mitochondrial dysfunction [35, 36].In addition, Vitamin E has been shown to protect against neurodegeneration by lowering oxidative stress [37].

The present study aims at exploring the homology analysis and association between protein-protein interaction network analysis of oxidative stress related proteins, i.e., SOD1, NOS2, IL6, PON1 and COX2 to elucidate the molecular basis of Alzheimer 's disease.

## 2. Data Sources

Disease genes are most often identified using: (1) genome-wide association or linkage analysis studies, (2) similarity or linkage to and co-regulation/co-expression/co-localization with known disease genes, and (3) participation in known disease-associated pathways or compartments. In this section, we discuss the AD genes/proteins data set and sources used for the construction of Phylogenetic tree and the Protein-Protein interaction. For this study purpose, we selected 13 oxidative genes/proteins that cause AD through (listed on the website http://www.genecards.org/ and the HEFalMp online tool – http://hefalmp.princeton.edu/). Figure 1 shows genes that are significantly associated with Alzheimer's disease in terms of oxidative stress. They are annotated from HUGO Gene Nomenclature Committee (HGNC), EntrezGene, Ensembl, GeneCards RNA genes and Human Chromosome 21 Database (Crow21) databases.

**Figure 1:** Genes that are most significantly connected to Alzheimer disease genes using the HEFalMp network and OMIM disease gene annotations (http://hefalmp.princeton.edu/disease/all_genes/55)



**Figure 2:** The genes that are most significantly connected to Alzheimer disease genes using the HEFalMp network and OMIMdisease gene annotations (http://hefalmp.princeton.edu/disease/all_genes/55). The gold bars to the left of APP and APOE indicate that both genes were annotated Alzheimer disease according to OMIM. doi:10.1371/journal.pcbi.1002816.g006

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## 3. Methodology and Algorithm

The In the present study, Protein-Protein Interaction analysis of oxidative stress proteins of Alzheimer's disease was implemented in a modular manner. It was divided into four modules. The procedure is as follows.
Step 1: Collect the Genes/Proteins responsible for AD from online Biological Databases
Step 2: Construct the Phylogenetic tree for AD proteins
Step 3: Construct the Protein-Protein Interaction network for T2D proteins
Step 4: Identify the association between the proteins.

## 4. Results and Discussions

Multiple sequence alignment was performed to the selected 13 AD causing proteins by submitting corresponding proteins in FASTA format to phylogeny tool, i.e., http://www.phylogeny.fr. The result of alignment is obtained in the form of a phylogram. Figure 3 shows the phylogram tree construction of AD proteins. The phylogram displays the

sequential relationship of proteins along with the scores that represent the distance between protein sequences.
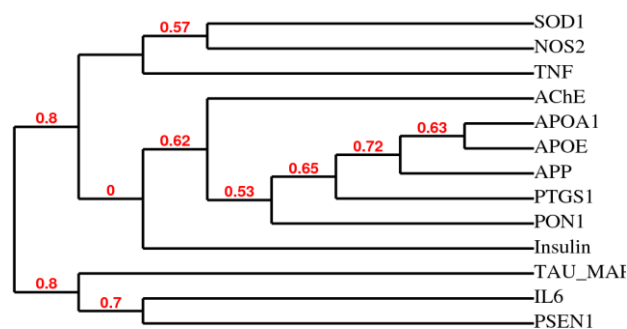


**Figure 3:** Phylogram tree for AD proteins.

## 5. Conclusions and Further Recommendations

Oxidative stress plays a crucial role in the pathogenesis of Alzheimer's disease. In the present work, we aimed to explore the evolution and interaction analysis to arrive at the relationship and association between oxidative stresses related AD proteins. We applied the data mining, text mining, evolution analysis and protein-protein interaction network analysis to identify the proteins that are most likely to cause AD. In the future, studies of this nature may pay way for in-silico protein-protein interaction experiments that can be extended to develop new therapeutic interventions for AD. The results of the study will be helpful in drug discovery and testing of particular disease requires preclinical and clinical trials.

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