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Gene Analysis And Protein-Protein Interaction study of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a disorder that causes degeneration of the cells in the brain and it is the main cause of dementia, which is followed by a decline in thinking and independence in personal daily activities. AD is considered a multifactorial disease: two main hypotheses were proposed as a cause for AD, cholinergic and amyloid hypotheses. Additionally, Many risk factors play a role in the disease such as increasing age, genetic factors, head injuries, vascular diseases, infections, and environmental factors. Currently, there are only two classes of approved drugs to treat AD, cholinesterase enzyme inhibitors and N-methyl d-aspartate (NMDA) antagonists. These medications only work to treat the symptoms of AD; they do not treat the underlying cause of the disease. In order to create effective treatments that can slow or alter the progression of AD, the main research focus today is on understanding AD pathology by focusing on a number of mechanisms, such as abnormal tau protein metabolism, beta-amyloid, inflammatory response, and cholinergic and free radical damage. Using bioinformatic methods, an effort has been undertaken in this research to identify the proteins connected to AD and extract information on their interactions. These might serve as pharmacological targets.

Keywords: Alzheimer's disease; neurodegeneration; risk factors; tau protein; β-amyloid peptide, interactome.

Introduction

Alzheimer disease is a loss of functional ability, which is caused by the degenerative brain disease. Although less prevalent types of the disease manifest earlier in adulthood, this disorder typically manifests in individuals older than 65. The most prevalent form of dementia, Alzheimer's disease (AD), which bears the name of the German psychiatric Alois Alzheimer, is characterised by neuritic plaques and neurofibrillary tangles. This is because amyloid-beta peptide (A) builds up in the medial temporal lobe and neocortical structures, which are the most commonly affected parts of the brain [9, 17].

Alzheimer's patients may become disoriented or confused. Even routine tasks like doing the laundry and other household chores can be challenging. Sometimes it can be difficult to recall names of people and objects[1]. Affected individuals increasingly require help with dressing, eating, and maintaining personal hygiene. As their disease worsens, some Alzheimer's patients have behavioural and psychological changes and struggle to connect in a way that is acceptable to others. Additional typical symptoms include agitation, restlessness, disengagement, and language loss. People typically need complete treatment when their condition is at an advanced stage. The disease can progress from 1 to 25 years, however affected people typically live for 8 to 10 years from the onset of symptoms. After the age of 80, the survival rate for people who are diagnosed is lower than it is for those who are diagnosed earlier in life. Pneumonia, starvation, or generalised body wasting are the usual causes of death (inanition).

Alzheimer's disease is a neurological, progressive illness that symbolises a deteriorating global health catastrophe. There are two main types of the illness: early onset (familial) and late onset (sporadic). Less than 5% of Alzheimer's disease cases had an early beginning, making it an unusual occurrence. It is caused by mutations in three genes (APP, PSEN1, and PSEN2) and is inherited in a Mendelian dominant manner.The early-onset form's symptoms and signs appear between the ages of thirty and sixty, whereas the late-onset form's symptoms and signs appear during or after the mid-sixties. Less than 10% of all occurrences of Alzheimer's disease are due to the late-onset variant, which is significantly more prevalent than the early-onset form.

Gene mutations that can be transferred from father to kid can contribute to early-onset Alzheimer disease in some situations. Early-onset familial Alzheimer disease is the result of this (FAD). This type of illness is brought on by mutations in the APP, PSEN1, or PSEN2 genes, according to research. When any of these genes is changed, the brain produces large levels of the deadly protein fragment known as amyloid beta peptide. Amyloid plaques are clumps of this peptide that can accumulate in the brain. Nerve cell death and the escalating signs and symptoms of this condition may be caused by an accumulation of toxic amyloid beta peptide and amyloid plaques. Changes in certain genes may be related to additional instances of early-onset Alzheimer disease [5].

According to certain data, those who have Down syndrome are more likely to get Alzheimer's disease. The disorder known as Down syndrome, which is marked by intellectual incapacity and other health issues, is brought on by a person having an extra copy of chromosome 21 in each cell at birth. People with Down syndrome have three copies of numerous genes, including the APP gene, in each cell as opposed to the typical two copies. Although there is no known link between Down syndrome and Alzheimer's disease, the increased risk could be due to cells producing too much amyloid beta peptide. Less than 1% of all Alzheimer's cases involve people with Down syndrome.

This particular form of Alzheimer's is not hereditary. Less is known about the aetiology of Alzheimer disease with late onset. Although clusters of instances have been observed in certain families, the late-onset type does not appear to run in families. This illness most likely results from changes in one or more genes combined with environmental and lifestyle variables. As a potential risk factor for the condition, the APOE gene has received substantial research. The e4 allele, a variation of this gene, is thought to enhance an individual's chance for late-onset Alzheimer disease[11].

One mutated gene copy in each cell is enough to cause early-onset familial Alzheimer disease, which is inherited in an autosomal dominant fashion. The mutated gene is typically passed down from one affected parent to the affected child. Uncertainty surrounds the hereditary pattern of late-onset Alzheimer's disease. One copy of the APOE e4 allele increases the risk of acquiring the disease, and two copies of the allele increases the risk even further. It is crucial to understand that the APOE e4 allele confers an elevated risk of Alzheimer disease, not the illness itself. Not everyone who carries the e4 allele also has Alzheimer's disease, and vice versa.

Many more genes have been associated with Alzheimer disease, and researchers are investigating the role that additional genes may play in Alzheimer disease risk. Genes Associated with disease POE, APP, PSEN1, PSEN2.

The advent of late-onset Alzheimer's disease has been linked to numerous genes. Numerous research have supported the existence of ABCA7, APOE, BIN1, CD2AP, CD33, CLU, CR1, EPHA1, MS4A4A/MS4A4E/MS4A6E, PICALM, and SORL1 as examples. Despite significant advancement over the previous three decades, over 50% of the heredity underlying the disease's late onset is still unknown. Finding the remaining genetic components that influence the emergence of late-onset Alzheimer's disease may lead to the identification of new targets for prevention and treatment, which could result in the creation of potent approaches to combat this deadly condition.

Other genes are:

- Estrogen Receptor Gene (ESR)
- vitamin D receptor (VDR)

Other genes' polymorphism associated with increasing the risk of AD include vitamin D receptor (VDR) gene polymorphism, which affects the affinity of vitamin D to its receptor and may cause neurodegenerative diseases and neuronal damage [6, 10]. Moreover, epigenetic factors like DNA methylation, histone, and chromatin modifications were demonstrated to be involved in AD [10].

Early Onset Alzheimers Genes: Inheritance from AD-HFE, NOS3, PLAU, A2M, MPO, APP Amyloid precursor protein (APP; 104760) gene mutation is the aetiology of Alzheimer disease-1 (AD1), which is found on chromosome 21q. Alzheimer's disease AD2 with late onset is connected to the APOE gene.

Alzheimer's type 3 with atypical plaques and spastic paraparesis: PSEN1 and APOE are associated genes. Early-onset familial AD-3 is caused by a heterozygous mutation in the presenilin-1 gene (PSEN1; 104311) on chromosome 14q24 (AD3).

Heterozygous mutation in the presenilin-2 gene (PSEN2; 600759) on chromosome 1q42 is the cause of Alzheimer disease-4 (AD4) .

APP is a type I transmembrane protein cleaved by α-, β-, and γ-secretase to release Aβ and other proteins and is encoded by the APP gene on chromosome 21. Thirty mutations have been found in the APP gene in which twenty-five of them are related to AD and cause an accumulation of Aβ with elevated amounts [16].

Using 365 markers, Sillen et al. performed a genome-wide linkage investigation on 188 AD patients from 71 Swedish families (average intermarker distance 8.97 cM). The entire family material was subjected to nonparametric linkage analysis, and the families were stratified according to whether or not APOE4 was present. The findings revealed that the APOE region was closely associated to the disease in these families (19q13). No linkage was discovered to chromosomes 9, 10, or 12 [18], and chromosome 5q35 had the next-highest lod score.

Reiman et al. (1996) used positron emission tomography (PET) to discover that 11 cognitively normal individuals between the ages of 50 and 65 who were homozygous for the APOE4 allele had decreased glucose metabolism in the same areas of the brain as people who likely had Alzheimer's disease. The prefrontal, parietal, posterior cingulate, and temporal regions were all impacted. These results offered preliminary proof that the APOE4 allele is a risk factor for Alzheimer's disease. Future testing of medicines to stave against Alzheimer disease may be facilitated by PET, according to Reiman et al. (1996) [13].

According to Romas et al. (2002), Caribbean Hispanics can develop familial AD at both early and late ages. Late-onset familial AD among Caribbean Hispanics was highly related with APOE4 compared to random AD[14].

A German family with earlyonset Alzheimer's disease with a PSEN1 gene mutation was documented by Hull et al. in 1998. The proband had complained of shortterm memory problems since the age of 43. His symptoms were first detected by family members even earlier, and they pinpointed the age of 38 as the turning point for deficiencies when he started to demonstrate an increase in speech stuttering and social withdrawal. There was a long history of dementia in the family. The start of dementia in this family ranged between 42 and 45 years old throughout the course of three generations[8].

According to Rippon et al. (2003), an African American family experienced early-onset psychosis and autosomal dominant dementia in the fifth decade. Two brothers were diagnosed with frontotemporal dementia (600274) after exhibiting personality problems, labile mood, language difficulties, psychosis, and primitive reflexes; nevertheless, they were also discovered to have memory impairment and neuropathologic evidence indicative of AD. The PSEN1 gene was mutated in both of the boys (104311.0006). According to reports, their father passed away from a similar ailment in his sixth decade[15].

Bird et al. (1988) described 5 German kindreds with an autosomal dominant early-onset form of Alzheimer disease. All families were descendants of a group of immigrants, known as the Volga Germans, who came to the United States between 1870 and 1920. Their ancestors had moved from Germany to the southern Volga region of Russia in the 1760s. All 5 were descendants of persons who originally lived in 2 small adjacent Volga German villages and shared several surnames known to have been present in the census records of those villages. There are more than 300,000 American descendants of the Volga Germans (see HISTORY)[2].

Further studies of this group by Levy-Lahad et al. (1995) found that the mean ages at onset for the families ranged from 50.2 to 64.8 years. Other than the relatively early age at onset, AD in the Volga group was clinically and pathologically indistinguishable from typical AD. Bird et al. (1996) reported that the mean age at onset in the Volga Germans is 54.9 years, mean age at death is 65.9 years, and mean disease duration is 11.3 years. These findings contrasted with families with chromosome 14-linked AD (AD3; 607822), in which the mean age at onset is 44.8 years, mean age at death is 52.6 years, and mean disease duration is 7.6 years. Bird et al. (1996) concluded that chromosome 1-linked AD (AD4) is characterized by a later age of onset that overlaps with the more common sporadic form of the disease [2, 3].

Finckh et al. (2000) reported a family in which 3 sibs with a mutation in the PSEN2 gene (600759.0006) were affected with early-onset AD and 2 sibs with the mutation were not affected. The affected sibs had onset at ages 44, 50, and 58. The disorder was characterized by anxiety, irritability, memory deficits, and impairment of language and attention. Two patients developed seizures and myoclonic jerks. Autopsy of 1 patient showed diffuse cortical atrophy, senile plaques, and neurofibrillary tangles. Finckh et al. (2000) noted that there may be variable age at onset, reduced penetrance, or other genetic disease modifiers [7].

Piscopo et al. (2008) observed beta-amyloid plaques and neurofibrillary tangles, but also found diffuse deposition of Lewy bodies throughout the brain. The findings added complexity to the phenotypes associated with PSEN2 mutations[12].

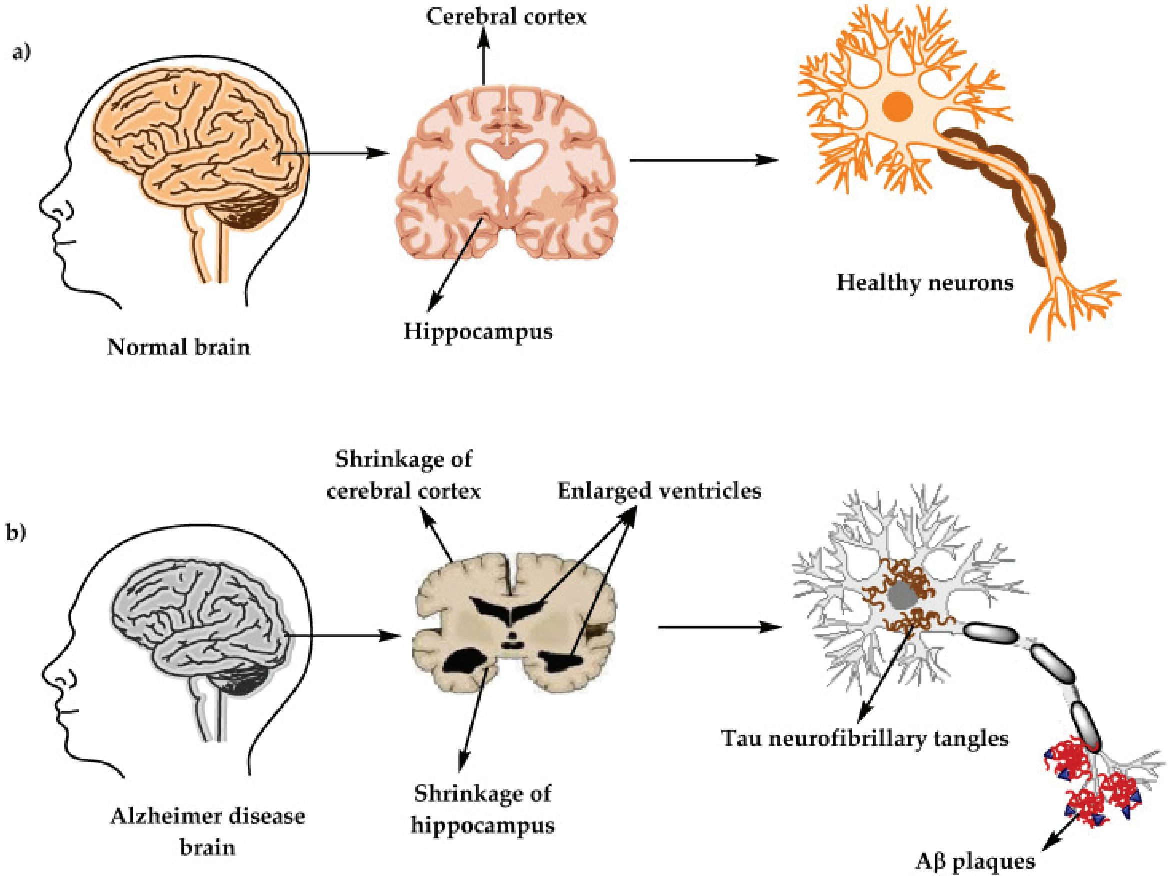


Figure: The Physiological structure of brain showing healthy brain and AD Brain[18]

Treatment

Currently, Alzheimer's disease cases worldwide are reported to be around 24 million, and in 2050, the total number of people with dementia is estimated to increase 4 times. Even though AD is a public health issue, as of now, there is only two classes of drugs approved to treat AD, including inhibitors to cholinesterase enzyme (naturally derived, synthetic and hybrid analogues) and antagonists to *N*-methyl D-aspartate (NMDA).

A patient suspected to have AD should undergo several tests, including neurological examination, magnetic resonance imaging (MRI) for neurons, laboratory examinations such as vitamin B12, and other tests besides the medical and family history of the patients [17]. Vitamin (vit.) B12 deficiency has been long known for its association with neurologic problems and increasing risks of AD, according to some studies. A special marker of vit. B12 deficiency is elevated homocysteine levels, which can cause brain damage by oxidative stress, increasing calcium influx and apoptosis. Diagnoses of vit. B12 deficiency can be done by measuring serum vit. B12 level alongside complete blood count and serum homocysteine levels tests.

Methodology

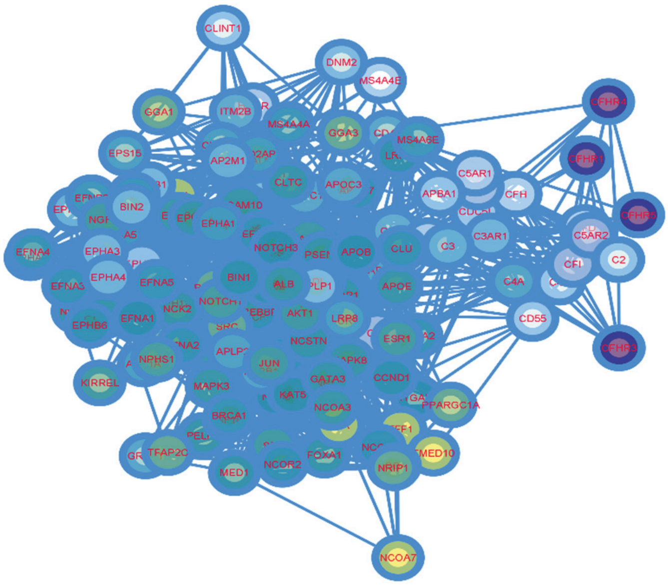
Go to the NCBI and find the proteins involved in Alzheimer's disease. Now Go to the String database and create the string network. Do K-means Clustering on the data. Then extract the interactome. Now use Cytoscape tool version 3.8.2 for network analysis. Construct the statistical data and calculate the value of degree of centrality. Higher the degree of centrality higher the interactions. Find the gene having highest degree of centrality using Cytoscape tool. Select the top 15 genes and construct a table. Get the nodes and edges. Plot the regression graph and scatter plot.

Results

Got the interaction network from cystoscope tool.

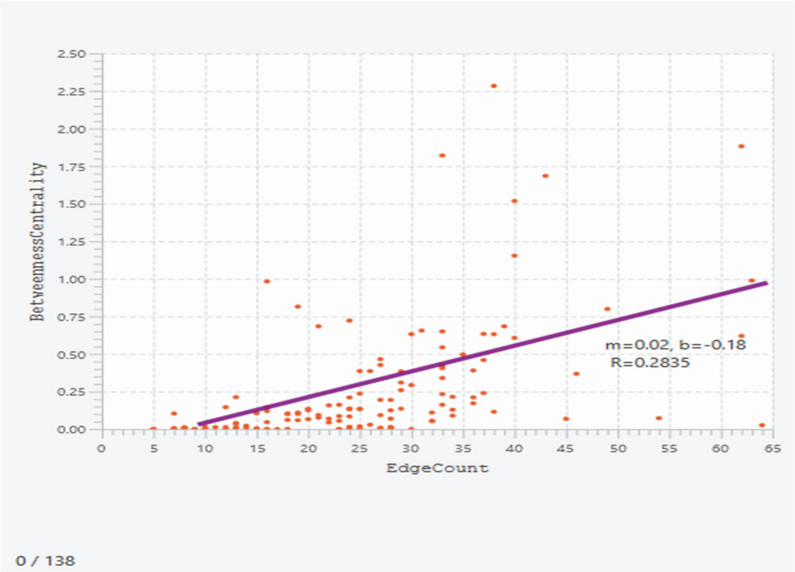
name	ClosenessCentrality	EdgeCount	Indegree	Outdegree
AKT1	0.637755	64	1	63
NOTCH1	0.681818	63	55	8
APP	0.625	62	17	45
SRC	1	62	59	3
ALB	0.58216	54	2	52
APOE	0.588889	49	14	35
PSEN1	0.5625	46	41	5
ADAM10	0.590909	45	1	44
EPHB2	0.538462	43	27	16
EPHA1	0.472222	40	16	24
CTNNB1	0.606061	40	8	32
ESR1	0.676056	40	12	28
MYC	0.658537	39	25	14
CLU	0.493151	38	24	14
EP300	0.690141	38	8	30
JUN	0.655172	38	18	20
PSEN2	0.533333	37	33	4

Got the protein interactome from cytoscape tool. The method used have enabled us to observe the wide network consists of one mighty network comprising of 138 nodes and 567 expected number of edges with a average node degree 24.5. Average local clustering coefficient is equal to 0.621. These are connected by nodes and various detached small networks. In our study AKT1 and SRC are the protein which has highest interactions in the network. These can be the potential drug target.



Scatter and Regression plot

Showing highest interaction between proteins with R=0.2835.



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