# Identification of Common Target Proteins for Multiple Neurodegenerative Disorders and Reconstruction of Disease Pathway

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## ABSTRACT

Neurodegenerative disorders are the disorder caused by the deterioration of certain nerve cells (neurons). Changes in these cells cause them to function abnormally, eventually bringing about their death. There are following six major neurodegenerative disorders which are most common in human: Alzheimer's disease, Prion disease, Parkinson's disease, ALS (Amyotrophic Lateral Sclerosis), DRPLA (Dentatorubropallidoluysian atrophy) and Huntington's disease. It is observed that there are some genes/proteins which are interlinked with all mentioned neurodegenerative disorders including some other diseases. A common pathway was constructed for neurodegenerative disorders taking Alzheimer's disease as the centre of the study because this disease is more common and well studied, and it is found that there are many genes or proteins in this disease which are interlinked with all mentioned neurodegenerative disorders including two more diseases, Alexander disease and Pick's disease. Therefore the reconstruction of common pathway with eight neurodegenerative diseases will add the significance of pre-existing pathways and disease targets.

## Keywords

Neurodegenerative disorders, KEGG, pathway studio 4.0

## 1. INTRODUCTION

Neurodegenerative disease is a term used for a wide range of acute and chronic conditions in which neurons and glial cells in the brain and spinal cord are lost [1]. The brain and spinal cord are composed of neurons that do different functions such as controlling movements, processing sensory information, and making decisions [2].

the pathway of Neurodegenerative disorders and individual pathways of different NDs like Alzheimer's disease, Prion disease, Parkinson's disease, Amyotrophic lateral sclerosis, Dentatorubral-pallidoluysian atrophy (DRPLA), and Huntington disease (HD) which are available on KEGG(Kyoto Encyclopedia of Genes and Genomes) has been studied and it is found that there are some proteins or genes which are common in more than one diseases and are also responsible for some other NDs like Alexander disease and Pick's disease.

Following six diseases and their interlinking genes/proteins have been studied for reconstruction of common disease pathway.

**Alzheimer's disease (AD)** is named after Dr. Alois Alzheimer, a German doctor. Alzheimer's disease (AD) is a progressive, neurodegenerative disease characterized in the brain by abnormal clumps (amyloid plaques) and tangled bundles of fibers (neurofibrillary tangles) composed of misplaced proteins [3]. Age is the most important risk factor for AD; the number of people with the disease doubles every 5 years beyond age 65. [4]

**Prion diseases** belong to group of progressive conditions that affect the nervous system in humans and animals [5]. In people, prion diseases impair brain function, causing memory changes, personality changes, a decline in intellectual function (dementia), and problems with movement that worsen over time. The signs and symptoms of these conditions typically begin in adulthood, and these disorders lead to death within a few months to several years [6].

**Parkinson disease**, first described by James Parkinson in 1817, is a growing national problem, with more than half a million Americans affected at any one time. Most people are over 50 years old when the disease appears, although it can occur in younger patients [7]. It is a neurodegenerative disease that manifests as a tremor, muscular stiffness and difficulty with balance and walking [8]. A classic pathological feature of the disease is the presence of an inclusion body, called the Lewy body, in many regions of the brain. [9]

**Amyotrophic lateral sclerosis** (ALS), often referred to as "Lou Gehrig's disease," is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord. Motor neurons reach from the brain to the spinal cord and from the spinal cord to the muscles throughout the body [10].The progressive degeneration of the motor neurons in ALS eventually leads to their death [11]. When the motor neurons die, the ability of the brain to initiate and control muscle movement is lost. With voluntary muscle action progressively affected, patients in the later stages of the disease may become totally paralyzed [12].

**Dentatorubral-pallidoluysian atrophy** (DRPLA) is a hereditary movement disorder associated with chorea, myoclonus, seizures, ataxia, and dementia. Due to an overlap of symptoms, DRPLA may be included in a differential diagnosis with Huntington's disease (HD) [13]. Molecular

testing and pathological examination are often used to distinguish HD from DRPLA because of the overlapping symptoms. Patients with an HD phenotype that test negative for an HD allele should be considered for testing for DRPLA. [14]

DRPLA progressively affects the cerebellar and pallidal outflow pathways. Tissue specificity seems to be directly related to particular gene products in HD and DRPLA [15]. For example, in DRPLA neuronal loss occurs prominently in the dentate nucleus, rubrum, globus pallidus and Luys' body, while in HD the loss of neurons is most commonly found in the caudate and putamen.

**Huntington disease** (HD) is a neurodegenerative disease that affects approximately 1 in 10,000 individuals of European decent and is characterized by progressive motor impairment and dementia [16]. HD is associated with an expansion of a CAG tandem repeat in exon 1 of the IT-15 gene on 4p16.3. HD is a dominant disorder with complete penetrance when the CAG repeat length > 40 [17]. Alleles with between 27 and 35 CAG repeats have never been shown to be associated with the HD phenotype, but are at risk to expand to disease alleles when passed onto offspring. [18]

**Alexander disease** is one of a group of neurological conditions known as the leukodystrophies, disorders that are the result of abnormalities in myelin, the "white matter" that protects nerve fibers in the brain [19]. Alexander disease is a progressive and usually fatal disease. The destruction of white matter is accompanied by the formation of Rosenthal fibers, which are abnormal clumps of protein that accumulate in non-neuronal cells of the brain called astrocytes.[20]

**Pick disease** (named after Arnold Pick) is a progressive dementia defined by clinical and pathologic criteria. Unlike Alzheimer disease and other dementias that present with cognitive deficits localized to the posterior (parietal) cortex, Pick disease typically affects the frontal and/or temporal lobes. [21]

# 2. METHODOLOGY

For reconstruction of the new common pathway in PATHWAY STUDIO 4.0 (http: //www. ariadnegenomics.com) software was used. By detailed study of the individual disease pathways and common neurodegenerative disease pathway, it was identified that there are following proteins which are interlinked with more than one disease fig. [1]:

NGFR, APLP1, GFAP, BCL2, HSPA5, MAPT, FBXW7, CASP8, CASP3, CASP6, CASP7, CASP1, GRB2, GAPD, APBA1, BCL2L1.

## 2.1 Pathway studio

Pathway Studio 4.0 is a desktop application for visualization and analysis of biological pathways. It has been developed by Ariadne Genomics, Inc. Rockville, Maryland. Pathway Studio helps you to interpret your experiment results in the context of pathways, gene regulation networks, and protein interaction maps. Using curated and automatically created databases, the software identifies relationships among genes, small molecules, cell objects and processes, builds networks, and creates the publication-quality pathway diagrams.

The software is supplied with the ResNet database, generated by the MedScan automated text mining tool from the entire PubMed and other public sources. The software can also work with a number of public and commercial databases such as KEGG, BIND, GO, and the PathArt database of curated signaling and disease pathways.

Using the Pathway Studio databases one can conveniently organize and effectively manage a large amount of biological data. Database objects can be organized into arbitrary number of folders and subfolders.

**Steps and Procedure**

a. Downloading Database-
b. Importing Protein List-
c. Build Pathway-
d. Edit Pathway-
e. Save Pathway –

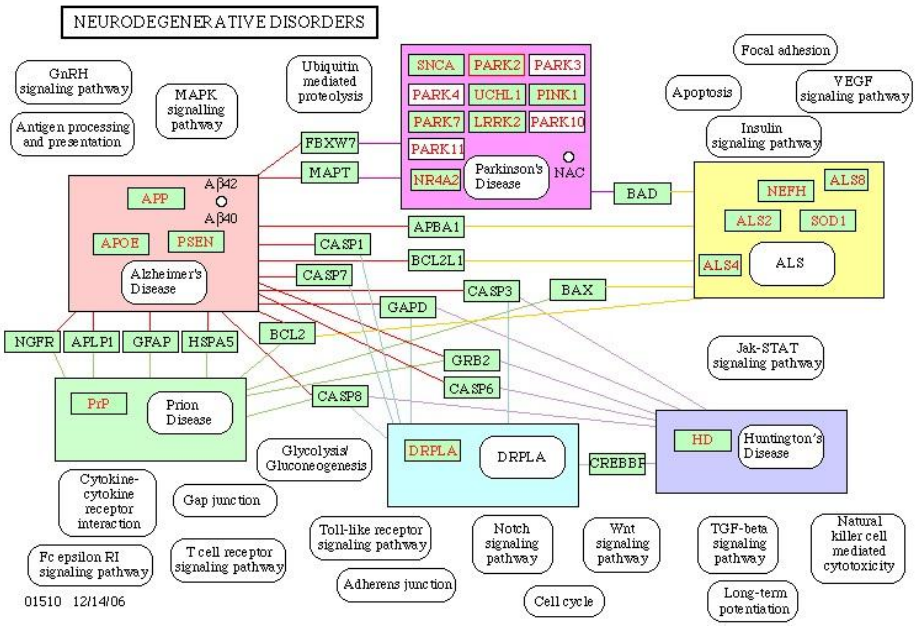


**Figure 1 .Pathway of neurodegenerative disorders**

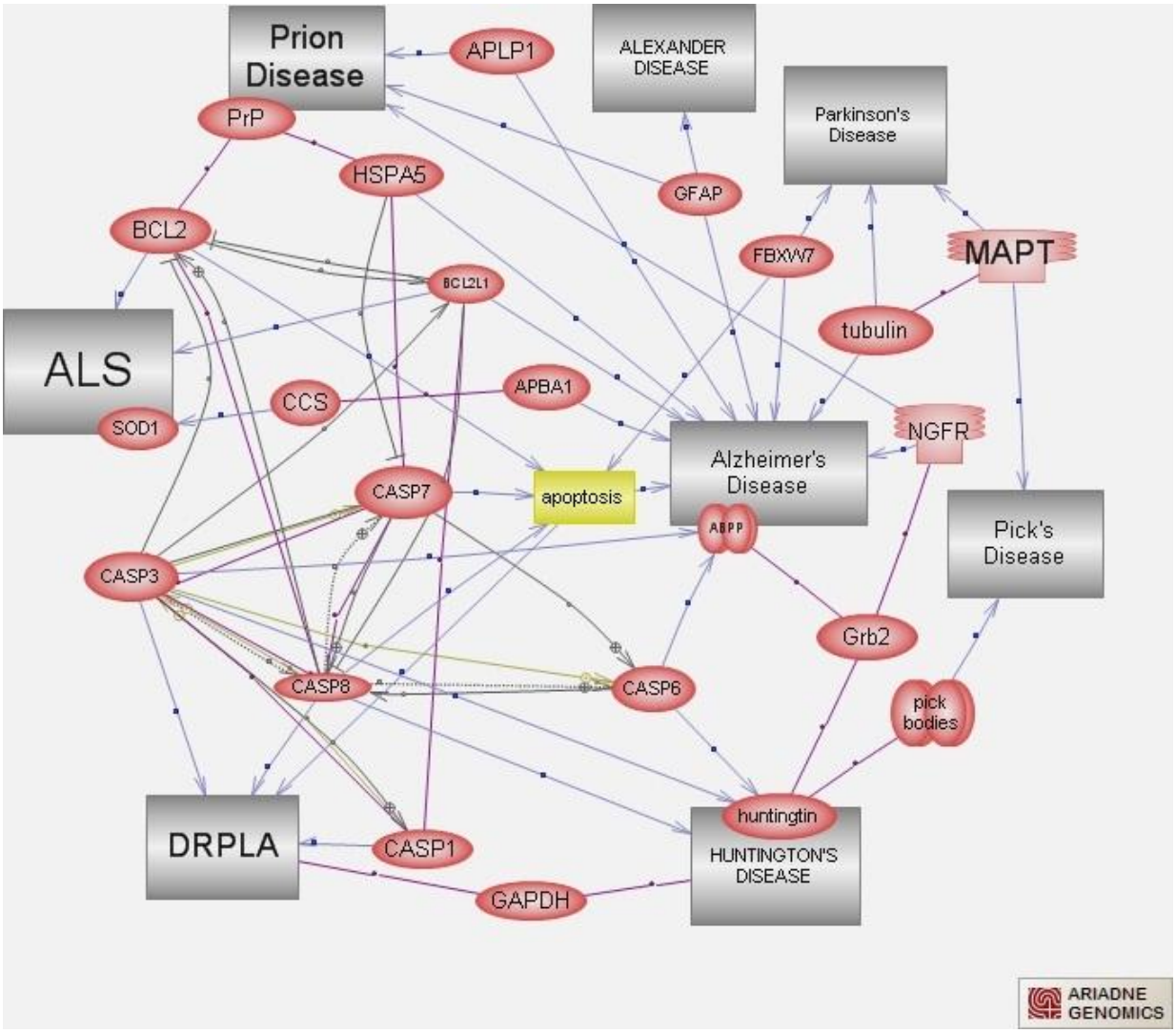


**Figure 2: Neurodegenerative disease pathway**

## 3. RESULTS AND ANALYSIS

The GFAP and MAPT is the responsible gene of Alexander disease and Pick disease respectively and these two disease have been added in the newly constructed common pathway using Pathway Studio Software (http://www.ariadnegenomics.com), a program that generates pathways of interaction based on a repository of findings from the literature and other databases.

In the newly constructed pathway it is shown that GFAP is inte4rlinked with Alzheimer disease, Prion disease and Alexander disease and MAPT is interlinked with Alzheimer disease, Parkinson disease and Pick disease. Fig.[2]

## 4. Conclusion

This pathway is important and useful in many sense like there may be identified a common and suitable drug for more than one neurodegenerative disease because there are many proteins which are common in three mentioned diseases. In this pathway there are eight neurodegenerative disease and the pre available pathway for neurodegenerative disease has only six diseases (in KEGG), two (Alexander disease, Pick Disease) extra diseases are added in this pathway.

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