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Identification of common therapeutic targets for selected neurodegenerative disorders: An *in silico* approach

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ABSTRACT

Neurodegenerative disorders (NDs) are a heterogeneous group of disorders generally characterized by a profound decrease in the size and volume of the human brain due to death of neurons. These disorders include a variety of progressive disorders that result in cognitive and/or motor degradation. The present study was conducted to identify common potential targets for multi-neurodegenerative diseases. To accomplish this, we have selected six common neurodegenerative diseases, Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), Prion disease and Dentatorubral-pallidoluysian atrophy (DRPLA) for identification of common regulatory target proteins. A total of sixteen common proteins were identified as target proteins by disease pathway analysis and previous studies based on their association with more than two NDs, including AD. An interaction network of each of the sixteen target proteins was then constructed against causative proteins selected from all six NDs by using the STRING 9.1 program. Pathway analysis and the protein–protein interaction network suggested that CASP-3 and CASP-8 were associated with the maximum number of selected NDs and may therefore be the most potent target proteins for treatment of multi-neurodegenerative diseases.

1. Introduction

Neurodegenerative diseases (NDs) are characterized by a profound reduction in the size and volume of the brain due to death of neurons as well as a variety of progressive disorders that result in cognitive and/or motor deterioration [1].

Common characteristics among neurodegenerative diseases have implications that influence the prevention of disease and development of effective therapies. NDs share many common features including late appearance in life, neuronal loss and synaptic abnormalities [1]. Another common feature of NDs is the formation of toxic protein aggregates [2–4]. Most NDs share common molecular mechanisms, such as mitochondrial dysfunction, neuronal apoptosis, oxidative stress and impaired protein homeostasis. Genetic mutations (SOD1, parkin, huntingtin), protein misfolding and aggregation (Lewy bodies, Amyloidβ, neurofibrillary tangles), mitochondrial dysfunction and caspase-mediated apoptosis are present in very different neurologic disorders [5]. A common molecular feature of NDs is intracellular or extracellular occurrence of protein aggregates in fibrillar structures known as amyloids [6,7].

Mutations in about 100 neurodegenerative disease proteins cause familial forms of NDs [8–10]; however, the mechanisms by which these mutations induce disease are largely unknown. In some diseases, such as HD and DRPLA, a family history of the disease can be ascertained in almost every case [10], whereas in others, such as AD [11], PD [12] and ALS [8], about 1–10% of all cases are inherited.

The identification of all these similarities in the pathogenesis of NDs facilitates targeting of certain genes for intervention of multiple NDs [13]. Although many studies have investigated individual neurodegenerative diseases, few have focused on common

Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; HD, Huntington's disease; DRPLA, Dentatorubral-pallidoluysian atrophy; NDs, neurodegenerative diseases.

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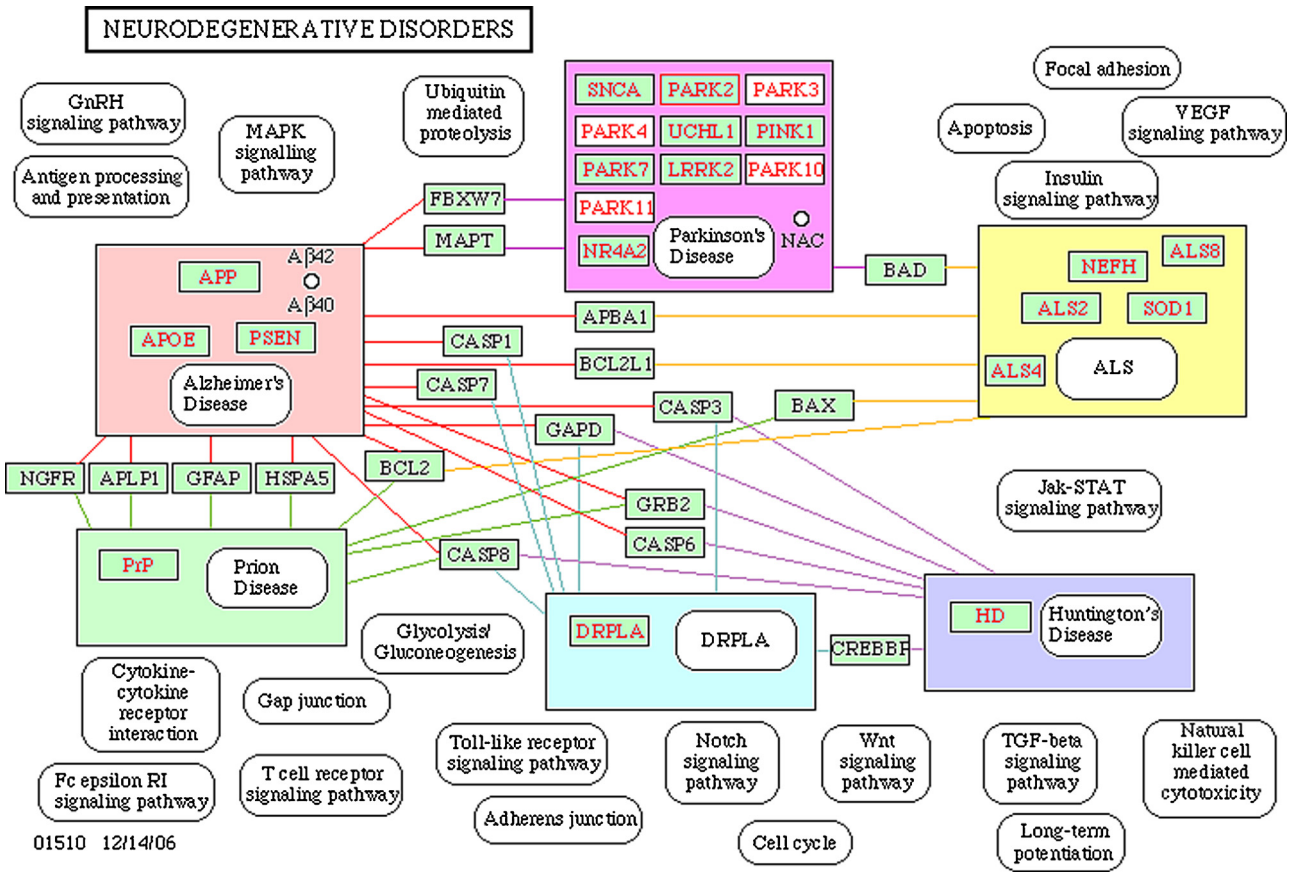

Fig. 1. Common pathway of neurodegenerative diseases [17].

regulatory proteins among neurodegenerative diseases or their protein–protein interaction networks [14,15].

Therefore, in this study, we focused on common regulatory proteins and protein–protein interaction networks associated with causative proteins of six well-known NDs, Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), Dentatorubral-pallidoluysian atrophy (DRPLA) and Prion disease (PRION). The objective of the study was to identify common regulatory targets involved in more than two selected NDs and provide a better understanding of the molecular pathogenesis of these NDs based on their protein interaction network. We identified and constructed protein–protein interactions maps in these six selected NDs and represented them as KEGG pathway maps of combined NDs [16]. Since AD is the most common and threatening disease, it was the focus of this study.

2. Methodology

2.1. Disease pathway retrieval of neurodegenerative diseases

The disease pathways of AD, PD, ALS, HD and PRION were investigated. Individual and common disease pathways were retrieved from KEGG (Kyoto Encyclopedia of Genes and Genomes) and from other pathway portals, which provided details regarding the regulatory proteins of the selected disease.

2.2. Selection of causative proteins from selected NDs and identification of common proteins

Major causative proteins from selected NDs were identified and selected for further protein–protein interaction analysis based on identified common target proteins. To accomplish this, we searched research articles from different resources to identify common target proteins involved in Alzheimer's disease along with other selected NDs. The individual disease pathway of each ND was used to generate a list of causative proteins: Alzheimer's disease (APP, PSEN1, PSEN2, APOE), Parkinson's disease (PARK2, SNCA, UCHL1, PARK7), ALS (SOD1, ALS2), Huntington's disease (HTT), Dentatorubral-pallidoluysian atrophy (ATN1) and Prion disease (PRNP). The protein–protein interaction network of these proteins was investigated using STRING 9.1 [ED highlight—consider defining this or specifying what it is. as described below (Fig. 1).

2.3. Protein interaction network construction and analysis using STRING

Common proteins were identified by literature survey and disease pathway analysis for the selected NDs. A common pathway for selected NDs, available from KEGG (http://www.genome.jp/kegg/pathway/hsa/hsa01510.html) [17], revealed 19 proteins as common proteins linked with more than two NDs. Here, we selected 16 common proteins that were found to be involved in regulation of more than two selected diseases, including AD. We selected all proteins involved in regulation of disease manifestation in NDs (Fig. 2).

An interaction network of each of sixteen identified target proteins was constructed against thirteen selected causative proteins (APP, PSEN1, PSEN2, APOE, PARK2, SNCA, UCHL1, PARK7, SOD1, ALS2, HTT, ATN1 and PRNP) using the Search Tool for the Retrieval of Interacting Genes (STRING) version 9.1.

STRING is a database of known and predicted protein interactions, including direct (physical) and indirect (functional)

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