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Review article

Gene networks in neurodegenerative disorders

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ABSTRACT

Three neurodegenerative diseases [Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease (PD) and Alzheimer's disease (AD)] have many characteristics like pathological mechanisms and genes. In this sense some researchers postulate that these diseases share the same alterations and that one alteration in a specific protein triggers one of these diseases.

Analyses of gene expression may shed more light on how to discover pathways, pathologic mechanisms associated with the disease, biomarkers and potential therapeutic targets.

In this review, we analyze four microarrays related to three neurodegenerative diseases. We will systematically examine seven genes (CHN1, MDH1, PCP4, RTN1, SLC14A1, SNAP25 and VSNL1) that are altered in the three neurodegenerative diseases.

A network was built and used to identify pathways, miRNA and drugs associated with ALS, AD and PD using Cytoscape software an interaction network based on the protein interactions of these genes. The most important affected pathway is PI3K-Akt signalling. Thirteen microRNAs (miRNA-19B1, miRNA-107, miRNA-124-1, miRNA-124-2, miRNA-9-2, miRNA-29A, miRNA-9-3, miRNA-328, miRNA-19B2, miRNA-29B2, miRNA-124-3, miRNA-15A and miRNA-9-1) and four drugs (Estradiol, Acetaminophen, Resveratrol and Progesterone) for new possible treatments were identified.

Contents

1. Introduction

The characteristics of three important neurophatological diseases: Amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD) and Parkinson's disease (PD) may coexist in individual patients. For example, all these diseases increased with age [1–3], all patients had dementia [4–6] and there were patients with both AD and ALS [7,8].

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These similarities, led us to ask the questions: Is there a common mechanism related to these diseases? Are there defects in one or more genes associated with these diseases?

The postulated mechanisms of these neurodegenerative diseases are: a lack of neurotrophic hormones [9], cytoskeletal alterations [10], possible interactions between environmental toxins and aging [11] or abnormalities of ubiquitin processing [12], but this has not been concluded.

In this context, our hypothesis is that there are many gene interactions and defects in these neurodegenerative diseases that may affect many pathways and only one specific alteration in a gene could be associated with one neurodegenerative disease. In the review, we examine seven genes affected in the three pathologies (CHN1, MDH1, PCP4, RTN1, SLC14A1, SNAP25 and VSNL1) and the association between them in order to better understand the basis of these diseases.

2. Main genes in neurodegenerative disease

In general the mean age onsets of these diseases are: 59.3, 61.9 and 71.9 years (ALS, PD and AD, respectively) [13], hereditary forms of ALS, PD and AD, account for less than 10% of all cases and inheritance is autosomal dominant [14–16]. In relation to the genes chromosome 21 was implicated in hereditary ALS, PD and AD as genes are located in this chromosome control the normal homeostasis of neurons [17–19].

On the other hand, many linked genes have been identified in relation to ALS [20,21], but the principal associated gene is superoxide dismutase 1 (SOD1) that is involved in intracellular detoxification of superoxide and this alteration produces an increase in toxicity and neuronal death [22], TAR DNA Binding Protein (TARDBP) is involved in mRNA processing and the modifications alter the RNA export, produced accumulation and ALS disease [23] and FUS RNA binding protein (FUS) participating in the initiation of transcription by interaction with RNA polymerase II and the TFIID complex and alteration produced formation of stress granules and ALS [24] and other emerging genes are Ubiquilin-2 (UBQLN2) that participate in the ubiquitin pathway, and alteration produced aberrant ubiquitination of protein in ALS [25] and chromosome 9 open reading frame 72 (C9orf72) that produces a massive expansion of a hexanucleotide repeat motif between non-coding exons (GGGCC)n causing ALS [26]. However the principal mechanism results in disease are unknown.

In relation to PD, there are also many genes that may be associated with this disease, but three genes are widely accepted: Alpha-synuclein (SNCA) mutations in this gene produce an increased number of copies with stable β sheets in this structure and induce the formation of toxic fibrils associated with faster disease progression [27]. Leucine-rich repeat serine/threonine-protein kinase 2 (LRRK2) has many mutations, some increase the kinase activity or GTPase activity and finally produced toxicity [28]. Vacuolar protein sorting-associated protein 35 (VPS35) mutations affect the normal endosomal sorting and results in the accumulation of intracellular α-synuclein-positive aggregates [29], but the specific mechanism of this disease remains unknown.

Finally, in relation with AD there are many genetic factors associated with this disease, but it is very complicated to indicate the most important. The principal associated genes are amyloid precursor protein (APP), mutations in this protein change the amino acid sequence lysine-methionine to asparagine-leucine this produces 2–3 fold higher the amount of Aβ42 peptide (amyloidogenic and more prone to aggregate, generated from APP by two cleavages by β and γ secretases) and increases its deposit and toxicity in the brain [30]. Presenilin 1 (PSEN1) and Presenilin 2 (PSEN2) other two genes related to AD are part of the γ-secretase complex, mutations in this enzyme produce more Aβ42 obtaining the same results as above with mutations in APP [31]. The last gene is apolipoprotein E (ApoE), mutations produces the same amino acid (Arginine) in position 112 and 158, this structure is a more efficient binding process of apoE4 (binds efficiently the Aβ peptide) thus enhances the deposition of the Aβ peptide and increases the toxicity in the brain [32]. Again the mutations in all these genes do not completely explain the principal mechanisms associated to produce AD.

In summary unfortunately all these studies have not revealed "THE GENE" that could provide an explication of the etiology of these neurodegenerative diseases. On the other hand, many researchers suggest that they share fundamental etiopathogenic aspects, mechanisms and genes [13,33–35]. In this sense, our hypothesis is that the three neurodegenerative diseases presented here share many pathological features since they share genetic level alterations. These modifications often involve disease-specific gene that is signature ones of these neurodegenerative diseases.

Studies of common genes might give a better understanding of the disease and are likely to shed light on important aspects of the three neurodegenerative diseases. This might result in discovering effective therapies for patients suffering from these diseases.

To analyze our idea, we selected seven shared genes (CHN1, MDH1, PCP4, RTN1, SLC14A1, SNAP25 and VSNL1) as shown in Table 1. Our strategy for the selection of the genes target was to analyze the data obtained from four microarrays of patients with neurodegenerative diseases. The first arrays detected the differential expression of 19,431 candidate genes in patients with SALS [36] and then this information was compared with 6375 expressed genes in patients with severe AD [37] and two microarrays with 1423 and 5197 genes expressed differently in patients with PD [38,39].

There are different databases for protein interaction, each database, show many and different protein targets. Our strategy for the target was to use five databases (IID, BioGRID, UniHI, APID and POINT) and select the most overrepresented target (Table 2). Here we will systematically examine the mechanisms of these genes on the neurodegenerative diseases.

Table 1
Altered genes in neurodegenerative diseases.

Gene	Full name	UNIPROT_ID	Gene ontology		
			Molecular function	Cellular component	Biological process
CHN1	N-chimaerin	P15882	SH3/SH2 adaptor activity	Cytosol	Positive regulation of signal transduction
MDH1	Malate dehydrogenase, cytoplasmic	P40925	L-Malate dehydrogenase activity	Cytosol	Small molecule metabolic process
PCP4	Purkinje cell protein 4	P48539	Calmodulin binding	Cytosol	Central nervous system development
RTN1	Reticulon-1	Q16799	Protein binding	Endoplasmic reticulum membrane	Neuron differentiation
SLC14A1	Solute carrier family 14 (urea transporter), member 1 (Kidd blood group)	Q13336	Urea channel activity	Integral component of plasma membrane	Transmembrane transport
SNAP25	Synaptosomal-associated protein 25	P60880	SNAP receptor activity	Membrane	Small molecule metabolic process
VSNL1	Visinin-like protein 1	P62760	Calcium ion binding	Cytosol	Calcium-mediated signalling