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Bioinformatics approaches to identify neurodegenerative diseases by next generation sequencing data

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Abstract
While there has been progress in the areas of cancer, cardiovascular, and metabolic diseases, the field of neurodegenerative diseases has proven to be extremely difficult. This is due, in part, to the fact that the aetiology of neurodegenerative diseases are unknown. According to research, patients with essential tremor frequently have neurological abnormalities such as bradykinesia, ocular movement anomalies, deficits in hand–eye coordination, mild dysarthria, gait ataxia, and possibly olfactory and hearing deficits. The advancement of next-generation sequencing (NGS) technologies is transforming medical genetics practice and revolutionizing the approach to heterogeneous hereditary conditions such as neurodegenerative disorders. The massive amount of genetic data generated by Next Generation Sequencing has had a significant impact on clinical diagnoses while also contributing to the discovery of molecular pathomechanisms central to these diseases.

Keywords: bioinformatics approaches, neurodegenerative diseases, generation sequencing (NGS)

Introduction

Neurodegenerative diseases, in general, and late-ons*et al*zheimer's disease (LOAD) in particular, involve a genetically complex and largely unknown ensemble of causative and risk factors, as well as complex feedback responses. With the advent of "high-throughput" transcriptome investigation technologies such as microarray and deep sequencing, sophisticated statistical and bioinformatics analysis methods are increasingly being combined with knowledge-based approaches such as Bayesian Networks or network and graph analyses. Such "integrative" studies are beginning to identify co-regulated gene networks that are linked to biological pathways and may modulate disease predisposition, outcome, and progression. Bioinformatics analyses of integrated microarray and genotyping data in cases and controls, in particular, reveal changes in gene expression of both protein-coding and small and long regulatory RNAs; highlight relevant quantitative transcriptional differences between LOAD and non-demented control brains; and show reconfiguration of functionally meaningful molecular interaction structures in LO. These can be measured as changes in connectivity in relevant gene network "hub nodes." (Zhang *et al*., 2013) [43].

Neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, amyotrophic lateral sclerosis, and prion disease are major public health concerns. Heavy metal exposure, such as manganese (Mn), may contribute to their development (Martins Jr. *et al*., 2020) [21].

Since the Human Genome Project decoded the Human Genome, techniques from bioinformatics, statistics, and machine learning have been critical in uncovering patterns in increasing amounts and types of data produced by technical profiling technologies applied to clinical samples, animal models, and cellular systems. Despite this, progress in unraveling biological mechanisms that are causally driving diseases has been slow, owing in part to the inherent complexity of biological systems. While there has been progress in the areas of cancer, cardiovascular, and metabolic diseases, the field of neurodegenerative diseases has proven to be extremely difficult. This is due, in part, to the fact that the aetiology of neurodegenerative diseases such as Alzheimer's and Parkinson's disease is unknown, making it difficult to identify early causal events (Hofmann-Apitius *et al*., 2015).

Diseases of the nervous system and oxidative stress

A number of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), have been linked to oxidative stress (Figure 1). Extensive oxidative damage to lipids, proteins, and DNA characterizes these diseases.

This damage can cause cell death through a variety of mechanisms, such as deactivating important processes or activating toxic cascades (Selley *et al*., 2002) [41].

Oxidative stress is caused by an imbalance in the pro-oxidant/antioxidant homeostasis, which results in the formation of toxic reactive oxygen species (ROS). ROS are produced by the interaction of oxygen with redox-active metal ions and play a normal metabolic role in cell signaling. ROS can be harmful to both metals, and ROS are strictly regulated. A, -synuclein, and SOD have all been linked to Alzheimer's disease, Parkinson's disease, and Lou Gehrig's disease, respectively. These proteins make up the majority of the deposits associated with these diseases. All of these proteins have been shown to interact with redox-active metal ions, resulting in the production of ROS (Pedersen *et al*., 1998) [28].

A will coordinate copper and iron to produce H2O2, which will be followed by the production of ROS via Fenton chemistry. -synuclein regulates vesicular dopamine uptake, and a breakdown in this process allows dopamine to accumulate in the cytoplasm. Dopamine coordinates iron and promotes the formation of reactive oxygen species (ROS). The destabilization of SOD's

active site allows for the corruption of this antioxidant enzyme, causing it to become pro-oxidant (Sayre, *et al*., 2001) [33].

Excitotoxicity is a side effect of calcium dysregulation caused by uncontrolled ROS. Drugs that target this toxicity (Memantine in Alzheimer's disease, Amantadine in Parkinson's disease, and Riluzole in ALS) provide only marginal clinical benefit. The antioxidant -tocopherol has shown clinical promise in the treatment of Alzheimer's disease. Inhibiting metal-mediated redox processes has demonstrated benefit in mouse models of AD and PD, as well as promising results in a small Phase II clinical trial for AD (Maynard *et al*., 2002, Barnham *et al*., 2004) [26, 1].

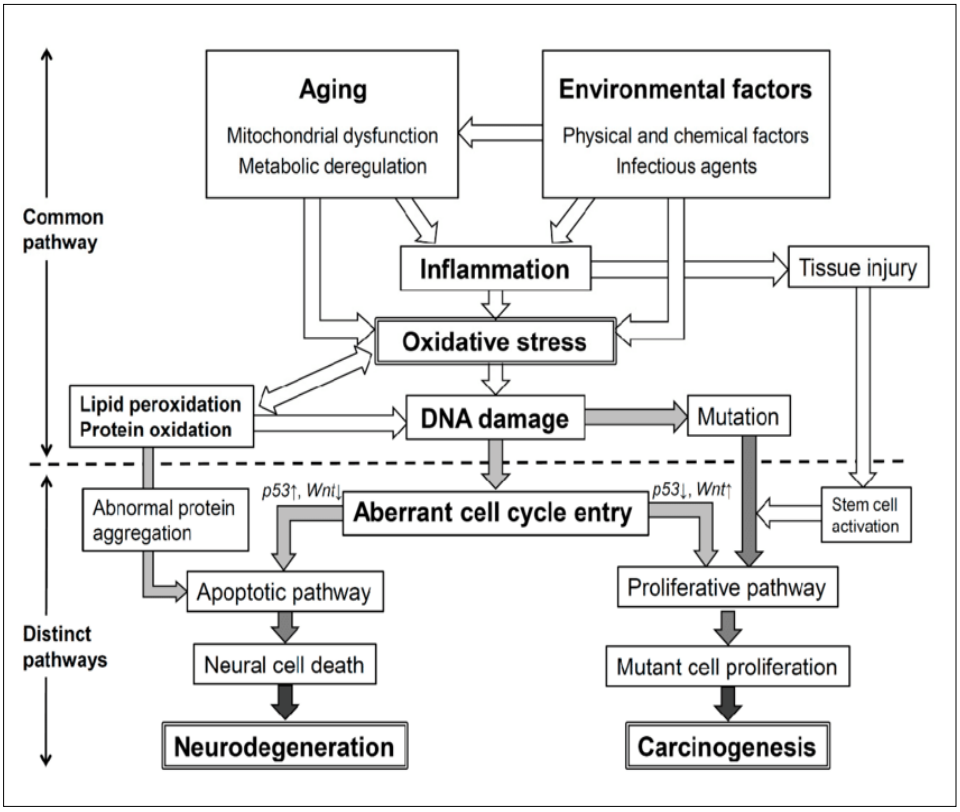


Fig 1: Roles of oxidative stress in neurodegenerative diseases and cancer.

Neurodegenerative disorder case studies

Rapid-eye-movement sleep behaviour disorder

Rapid-eye-movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by dream-enacting behaviors and loss of muscle atonia during REM sleep. RBD can be idiopathic or linked to a neurological disorder. According to the available data, RBD may be the first symptom of a neurodegenerative disease in some cases. The purpose of the study by these workers was to determine the frequency and nature of neurological disorders that developed in patients with idiopathic RBD at our sleep center (Iranzo *et al*., 2006) [10].

These researchers (Iranzo *et al*., 2006) [10] performed a detailed clinical history, complete neurological examination, parkinsonism rating scales, and neuropsychological tests on 44 consecutive patients (39 men and five women with a mean age of 74 years) with at least 2 years of clinical follow-up after a diagnosis of idiopathic RBD.

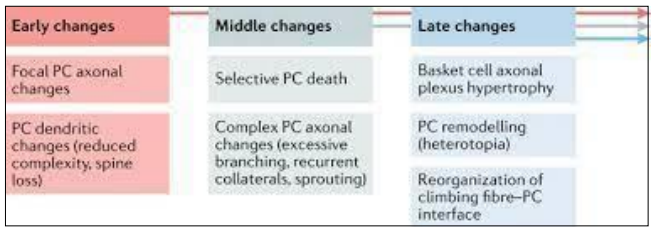
According to the studies (Iranzo *et al*., 2006) [10], 20 (45%) patients developed a neurological disorder after a mean of 115 years from the reported onset of RBD and a mean follow-up of 51 years from the diagnosis of idiopathic RBD at their sleep center. Parkinson's disease was discovered in nine patients, dementia with Lewy bodies in six, multiple system atrophy with predominant cerebellar syndrome in one, and mild cognitive impairment in four patients with visuospatial dysfunction. Patients with a longer clinical follow-up had a higher risk of developing a neurological disease (OR 1512, 95 percent CI 1105–2069; p=010).

According to their findings, RBD frequently precedes the development of a neurodegenerative disorder in people who present to sleep centers. Close monitoring of patients with idiopathic RBD may allow for the early detection of neurodegenerative disease. This discovery could be very useful when early effective treatment strategies and neuroprotective drugs become available (Iranzo *et al*., 2006) [10].

Essential tremor cognitive defects

Initially, essential tremor was thought to be a single-symptomatic movement disorder with no known CNS pathology. However, new research indicates that essential tremor is a slowly progressive neurodegenerative disorder primarily associated with cerebellar pathology (Table 1). According to research, patients with essential tremor frequently have neurological abnormalities such as bradykinesia, ocular movement anomalies, deficits in hand–eye coordination, mild dysarthria, gait ataxia, and possibly olfactory and hearing deficits. Essential tremor is linked to mild cognitive impairment, mood disorders such as depression and anxiety, and an increased risk of dementia.

Table 1: Essential tremor pathology: neurodegeneration and reorganization of neuronal connections (Louis and Faust, 2020) [18].



Several research groups have discovered pathological changes in the cerebellum of people who have essential tremor (ET) (Figure 2). Changes in Purkinje cell (PC) axons and dendrites, displacement and loss of PCs, changes in basket cell axonal processes, abnormal distribution of climbing fibre connections to PCs, and changes in GABA receptors in the dentate nucleus are all symptoms of ET. Some of the observed changes (for example, PC loss) may result in decreased GABAergic output from the cerebellum (Louis and Faust, 2020) [18]. Some ET pathological changes are likely to be primary and degenerative, while others may be compensatory responses aimed at restoring cerebellar GABAergic tone. Both PCs and neighboring GABAergic neurons (basket cells) in the brains of ET patients may increase their connections with PCs, resulting in rewiring and reorganization of neuronal connections within the cerebellum (Louis and Faust, 2020) [18].

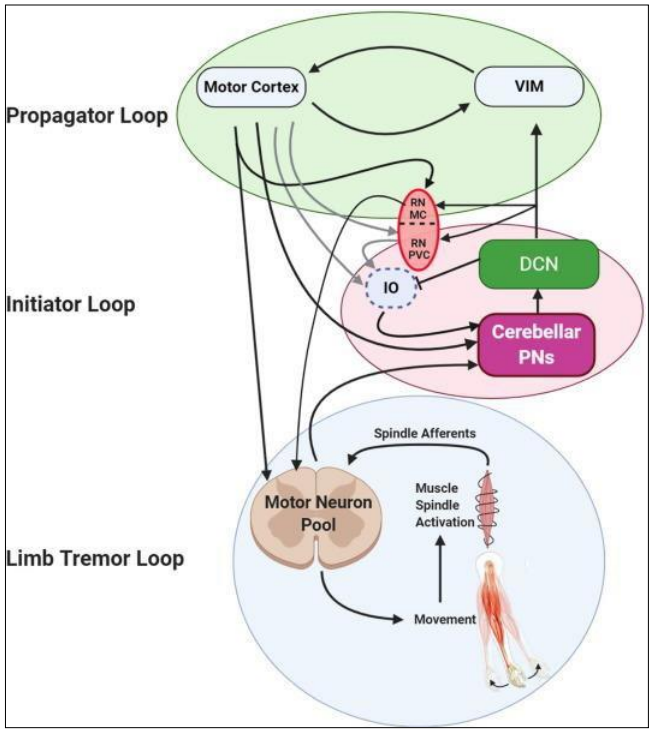


Fig 2: Cerebral driven essential tremor (Louis and Faust, 2020) [18]:

Bioinformatics Approaches to Identify Neurodegenerative Diseases By Next Generation Sequencing Data

The advancement of next-generation sequencing (NGS) technologies is transforming medical genetics practice and revolutionizing the approach to heterogeneous hereditary conditions such as neurodegenerative disorders (Nigro and Savarese, 2016) [27]. NGS panels are widely used in clinical diagnostics to identify genetic causes of various monogenic disease groups, such as neurometabolic disorders and, more recently, lysosomal storage disorders (LSDs). Many new challenges have been introduced by these new technologies, both in the laboratory and in bioinformatics, with consequences including new requirements for result interpretation and genetic counseling.

Network Analysis for Complex Neurodegenerative Diseases

The way complex disorders are investigated in biomedicine is undergoing a paradigm shift. The need for big data interpretation, in particular, has resulted in the development of pipelines that necessitate the collaboration of experts from various fields, including medicine, functional biology, Informatics, mathematics, and systems biology. The era of big data has arrived in biomedicine, and it is actively changing the way we approach and conduct research. Because of the increased size and power of biomedical studies, multi-center, international working groups have been formed to coordinate open access platforms for data generation, storage, and analysis. Pipelines for data interpretation, in particular, are being developed, and network analysis is gaining traction as a versatile approach to studying complex systems composed of interconnected multiple players (Table 2).

Table 2: Some open access, big data repositories. From Network Analysis for Complex Neurodegenerative Diseases (Manzoni *et al*., 2020)

Resource	Website	Details	Reference
Database of Genotypes and Phenotypes (dbGaP)	https://www.ncbi.nlm.nih.gov/gap	Catalogue of genetic datasets	Mailman *et al*., 2007
GWA catalogue	https://www.ebi.ac.uk/gwas	Catalogue of published GWA	Buniello *et al*., 2019
1000 Genomes	https://www.internationalgenome.org	Controls or general population human genome	The 1000 Genomes Project Consortium (2015)
NCBI	https://www.ncbi.nlm.nih.gov/genome	Open access genome browsers	SDaR. 2019
The Encyclopedia of DNA Elements (ENCODE)	https://www.encodeproject.org	Catalogue of non-coding elements	Davis *et al*., 2018
Kyoto Enciclopedia of Genes and Genomes (KEGG pathway)	https://www.genome.jp/kegg/pathway.html	Pathways repository	Kanehisa, and Goto, 2000

Sanger sequencing has assisted us in laying the groundwork for Next Generation Sequencing (NGS). When compared to other diseases, neurodegenerative diseases are the least curative in nature, and the only measures that can be taken are at the onset stages, which are easily treatable. This is where Next Generation Sequencing (NGS) comes in (Sehgal *et al*., 2017) [39].

The massive amount of genetic data generated by Next Generation Sequencing has had a significant impact on clinical diagnoses while also contributing to the discovery of molecular pathomechanisms central to these diseases. In the present day. Neurodegenerative diseases are becoming more common, but treatment options remain limited. With the introduction of Next

Generation Sequencing, there is hope for advancement in current techniques to target specific genes related to the disease that may be under or over expressed. The study of mutations in specific genes associated with diseases such as Alzheimer's (FAD, PSEN1, and PSEN), Parkinson's (PINK1-PARK6), ataxia (FXM, ATM), and Multiple Sclerosis (IL7R, IL2R, CD226, TKY2) broadens our perspective on these least curable diseases. Next Generation Sequencing has transformed the study of genomics and molecular biology because it is both cost effective and time efficient. NGS technologies are designed to generate short sequences with higher error rates. Even though the instrument is inexpensive, the overall cost of sequencing a single genome is prohibitively expensive. Because sequencing costs more per base than standard instruments, an overall infrastructure is still required (Kircher and Kelso, 2010) [12]. The current state of technology presents inherent challenges, particularly when dealing with massive amounts of data. However, massively parallel sequencing platforms and technological advancements have aided in the development of novel hope to some extent. More progress is currently desired in order to correctly understand and interpret data.

Conclusion

Neurogenerative diseases happens to all aged persons in one way or the other. Bioinformatics approaches to identify neurodegenerative diseases by next generation sequencing data will help to mitigate its effects as its fast and more accurate.

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