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Bioinformatics approaches using computational tools of Neurodegenerative Diseases

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ABSTRACT

More than 40 million people worldwide suffer from neurodegenerative disease (ND). Many of these diseases lack treatment to slow or stop their progression. This is mainly due to the challenge of releasing the co-occurrence of a wide variety of pathophysiological changes. The increase in many ND risk factors is age, highlighting the need of developing viable therapies for the world's ageing population. Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease are among the most often studied NDs (HD). Current technology and computing capabilities show an optimistic future that shows these changes, ND and progress. Network and graph analysis are examples of "high-throughput" research-based methodologies. Proposes accessible modular and pathway-oriented bioinformatics research methodologies that uncover possible biomarkers or treatment targets and bring fresh insights into the complicated pathophysiology of such diseases. This review focus on the technical and computational approaches and multiomic analysis will enable the discovery of new therapeutic strategies for these catastrophic diseases.

KEYWORDS: Neurodegenerative diseases, Huntington’s disease, Frontal dementia, biomarkers, Alzheimer’s disease, multi-omic.

1. INTRODUCTION

Neurodegenerative is a state where nerve cells die and eventually losses their function and cause complex and incurable disease. Typically, Neurodegenerative disorder is a broad term decipher various conditions, despite the fact that some of these illnesses have similar causes [1]. The disorders usually manifest themselves in elderly age, In the central nervous system, there is a slowly increasing clinical course and neuronal loss with regional specificity. There are thousands of neurodegenerative disorders, the majority of which are incurable, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease, as well as multiple sclerosis [2]. These disorders' pathophysiology vary, with some causing cognitive and physiological problems and others impacting a person's capacity to move, speak, and breathe [3]. In general, the risk of having Alzheimer's disease grows with age, and one in every eight people over the age of 65 has the condition. It is the most frequent type of dementia or mental decline in elderly people. Furthermore, 400,000 people have multiple sclerosis (MS), 30,000 have amyotrophic lateral sclerosis (ALS or Lou Gehrig's illness), and 30,000 have Huntington's disease [4]. Neurodegenerative disorders are complex diseases that are thought to involve a large variety of processes that operate at multiple levels. Deregulations at the molecular level [5], as well as flurried cell-to-cell interactions [6] and pathophysiological alterations at the organ level [7], are all possibilities.

Because neurodegenerative disorders impair the function of neuronal cells in the brain, they have devastating implications for patients and their families [8]. At the moment, innovative treatment options for Alzheimer's disease, Parkinson's disease, and Huntington's disease are still in the clinical trial phase, while commercially accessible and licenced medications mostly relieve symptoms without appreciably slowing disease progression. The United States Food and Drug Administration (US-FDA) recommended most prescribed medications for AD (memantine) and PD (levodopa) in the late 1970s [9]. There are no effective disease-modifying medications on the market right now. Tetrabenazine, the first FDA-approved treatment for HD, was approved in the late 2000s and remained the only choice until the FDA approved a chemically modified version of the medicine (deutetrabenazine). As a result, despite the best efforts of scientists, physicians, and pharmaceutical corporations, innovative therapeutics for neurodegenerative illnesses are still desperately needed. Beside this, the ever-increasing demand for the diagnosis and treatment for NDs, and the assurance that drug repositioning constitutes the effective drugs that are being tested for these diseases. In this review, the volitional neurodegenerative diseases includes Multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease (AD), and Lou Gehrig's disease (ALS) have all been renamed (Figure 1).

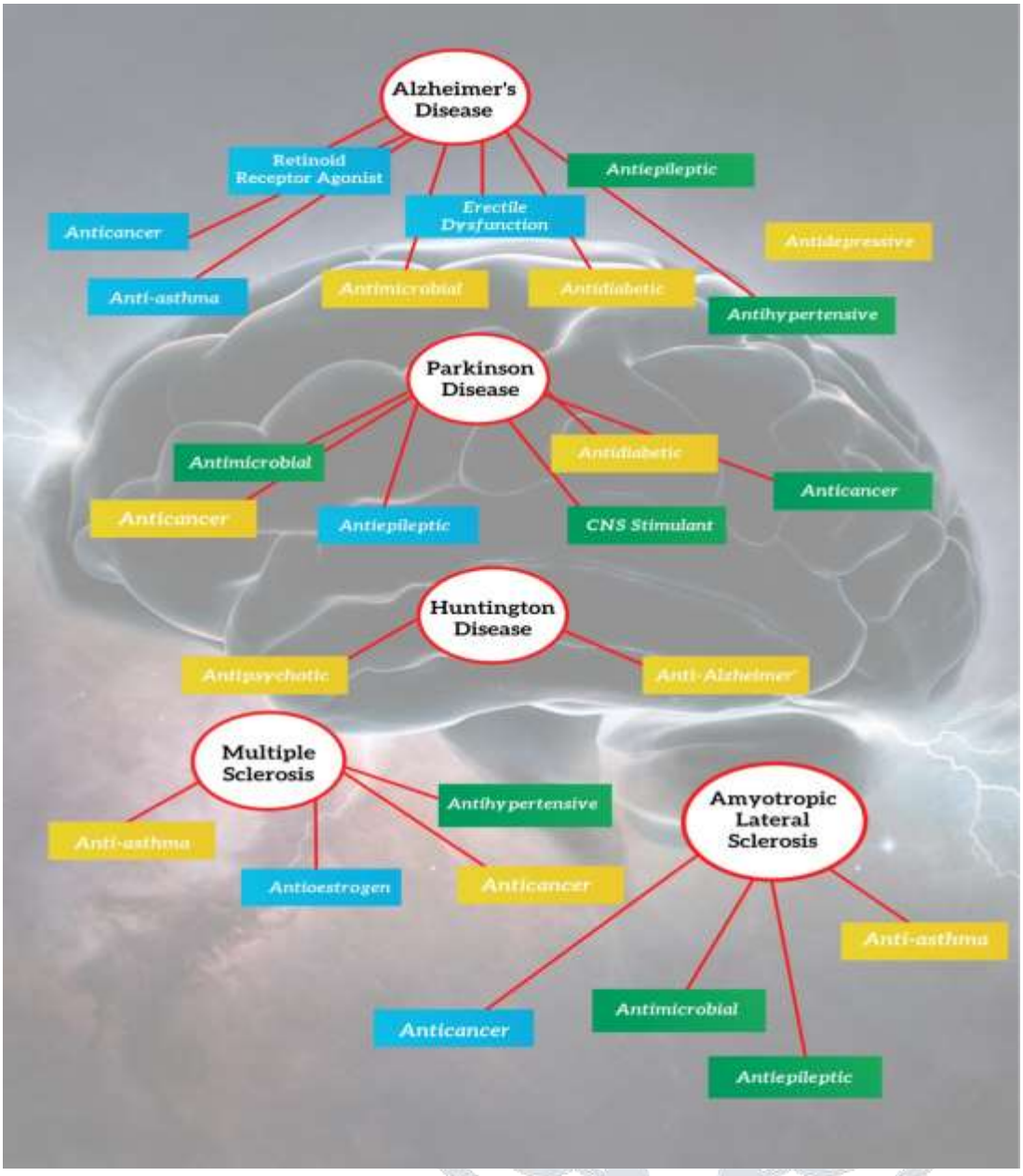

Figure 1: Synopsis of the diseases and repurposed drugs are demonstrated in this review.

In the case of HD, the most significant advancements have been seen in gene-based approaches focused at lowering the expression of the mutated protein as soon as possible. Tominersen (IONIS-HTTRx), a synthetic DNA oligomer developed with the help of Ionis Pharmaceuticals, was found to have a dose-dependent ability to lower the mutant HD-causing protein in 34HD patients who participated in random, double-blind, multiple-ascending-dose Phase 1-2a trials [10,11]. Genetic studies of Alzheimer's and Parkinson's disease have provided insight into the molecular pathways underlying disease genesis [12].and these mechanisms are not able to explain the wide range of pathologies which associates with periodic forms of NDs. Some of the molecular objectives are required to expand more knowledge of the diagnostic and therapeutic remedies of these diseases.

1.1. Differential Gene Expression (DGE) analysis

The modern approach have guide to a stronger understanding of altered molecular mechanisms within cells of the various organs of our body. Several developments have taken place in the field of genetics with new sequencing techniques that establish the genotypic aberrations using large bioinformatics databases [13]. Bioinformatics is an interdisciplinary field of applied science widely used in neurodegenerative research, especially in terms of discovering new targets and routes [14]. Prices for DNA genotyping on microarrays have decreased over the last decade, and sequencing has cleared the path for genome-wide association studies (GWAS)[15]. Large-scale genetic association studies have started to reveal the genetic architecture of neurodegenerative diseases. They discovered that disease risk is influenced by hundreds to thousands of genetic loci [16]. More than 25 genetic loci linked to Alzheimer's disease have been discovered by next-generation sequencing research, including rare variants like TREM2, UNC5C, AKAP9, and ADAM10 [17, 18]. The disorder is analogous to Parkinson's disease, where a genome-wide association study identified 28 risk variations across 24 genetic loci [19]. These loci can be utilised to generate individualised polygenic risk scores and serve as the foundation for genetic and genomic biomarker and discovery target [20, 21]. In European and Asian populations, genome-wide association studies (GWASs) have identified roughly 90 common genetic variants linked to PD risks [22, 23]. Aside from genetics, the possibility of RNA-based biomarkers has lately been investigated in Parkinson's disease research. Microarray and RNA-seq-based transcriptomics analyzes are a standard tool for measuring gene activity on a transcriptome level [24-31].

Imaging techniques such as positron emission tomography (PET), magnetic resonance imaging (MRI), and nuclear magnetic resonance imaging (NMRI) can be used to measure biomarkers (NMRI). Table 1 lists numerous neurodegenerative disease diagnostic indicators [32].

Table 1: A list of Alzheimer's, Parkinson's, Amyotrophic lateral sclerosis, and Huntington's disease genetic and biochemical diagnostic indicators.

Diseases	Genetic diagnostic markers	Biochemical diagnostic markers
Alzheimer’s Disease (AD)	Mutations in the precursor protein for amyloid Presinilin-1 is a kind of presinilin that is (gene mutations) Presinilin-2 is a kind of presinilin that is (gene mutations)	Plasma/CSF Aβ1-42 peptide CSF tau protein Phospho-tau

	Isoforms of ApoE Polymorphisms in the ApoE gene	
Parkinson's Disease (PD)	Mutations in the -synuclein gene Mutations in the PARKIN gene Mutations in the UCH-L1 gene Mutations in the PINK1 gene Mutations in the DJ-1 gene Mutations in the NR4A2 gene	Loss of Dopamine Transporter (DAT) Lewy bodies
Amyotrophic Lateral Sclerosis (ALS)	Mutations in the ALS2 gene Mutations in the NEFH gene Mutations in the SOD1 gene Mutations in the C9orf72 gene Variations in the FUS gene Mutations in the TARDBP gene	mGLUR2 SOD1 Glutathione 8OH2'dG Cytokines
Huntington's Disease (HD)	Mutations in the HTT gene	Growth hormones Cytokines Mglur2 SOD1 Glutathione

1.2. The emergence of non-coding RNAs

Variations in the gene expression of each protein-coding and small and long regulatory non-coding ribonucleic acids (ncRNAs) were discovered in a recent bioinformatics research using integrated microarray, next-generation sequencing (NGS), and genotyping data [33, 34]. IncRNAs classified as "regulatory" have a considerable impact on the expression and/or function of protein-coding genes [35].The latest study has shown that the microRNA (miRNA) is involved in the pathogenesis which makes it more suitable hotspot to explore and target it as anti-neurodegenerative therapeutic approach [36 The classification of gene expression profiles in pd for diagnostic purposes [37, 38], and its three types of non-coding RNAs, microRNA (miRNA), long non-coding ribonucleic acid (lncRNA), and circular RNA, are known as possible biomarkers (circRNA) [39,40]. MicroRNAs (miRNAs) and tiny RNA species (200 nucleotides) could directly regulate transcription by interacting with the promoter

region of transcribed genes [35]. The sensitivity of 24 miRNA studies attempting to discriminate between pd cases and healthy controls ranged from 56.7 percent to 96 percent, and their specificity from 63.3 to 92 percent [41-44]. There are many proof that lncRNAs plays a necessary role in development of brain and many molecular functions as regulating protein activities, modulating transcriptional motifs, altering RNA processing, and also known as precursor of small RNA and evidence suggest that the disruption of regulation of Huntington's disease (HD), Alzheimer's disease (AD), and Parkinson's disease (PD) are all caused by IncRNA. One possible aspect of lncRNA participation in neurodegenerative disorders is their ability to compete with endogenous RNAs (ceRNA). CeRNAs are transcripts with miRNA recognition elements in them (MREs). Pseudogenes [45] or lncRNAs [46] will be the culprits. Bioinformatics analysis has revealed that several lncRNAs with putative MREs are differently expressed in a variety of neurodegenerative disorders [47, 48]. This lncRNA affects many miRNAs, as well as several miRNA targets and protein expression, possibly explaining at least a portion of the large transcriptional differences caused by neurodegenerative illness.

1.2. Network building enhancing functional annotations

In monogenic illnesses, functional analysis of a single altered gene can reveal a mutation with a large effect size in a specific gene that works as a disease-causing and disease mechanism. The molecular mechanisms that reveal the intricacies of neurodegenerative disorders are difficult to track down because the genetic architecture is difficult to predict and needs simultaneous analysis of several causal indicators [49]. Although differential gene expression analysis (DGE analysis) solves this issue, it only does so for one gene at a time and does not account for gene connections. In this scenario, Insilco systems biology tools, such as network analysis, tie genes to one another using measured or expected interactions and provide an essential organisational structure that positions each gene in its molecular system. The ability to identify multiple levels of molecular organisation and revolutionise the translation of genetic information into a functional understanding of the molecular basis of diseases, such as known pathway annotations, protein interactions, and other molecular profiling data, is a significant advantage of network analysis over DGE analysis [24,25,50,51]. Networks, often known as graphs, are mathematical structures that are represented as a collection of data points. Edges (connections between objects) and nodes (connections between nodes) can also be used to illustrate networks (as symbolised into objects). In the context of a disease, each node represents a gene, nucleic acid, protein, enzyme, metabolite, or drug that is linked by a network of interactions, which are linked by a series of interactions that include physical, genetic, co-expression, and regulatory interactions, but are not limited to these. Other gene-expression regulators, including as microRNAs, non- coding RNAs, and epigenetic modifications, can be included in gene regulatory networks [52]. Edges between nodes are constructed mathematically [55]. GRNs are complex networks that are frequently built using statistical approaches based on inference algorithms (such as Bayesian, artificial neural, and Boolean networks, regression-based model, ordinal differential equation, and information theory) [53,54]. These methods find the probability of inversely regulated node pairs within large datasets (e.g., protein-DNA

interactions, gene expression, and transcription factors binding) and mathematically create edges between nodes [55]. These interactive maps can be used to reveal key genotype-phenotype correlations as well as disease-causing biological processes. Network biology, in particular, enables more holistic disease modelling assistance and aids in concentrating efforts on the most promising functional targets [52].

Table 2: Databases for creation of biological networks in NDs

Database	Link	Reference
NCBI	(https://www.ncbi.nlm.nih.gov/genome)	[56]
Ensembl	(https://www.ensembl.org/)	[56]
Genome Reference Consortium	(https://www.ncbi.nlm.nih.gov/grc/data)	[57]
UCSC	(https://genome.ucsc.edu/)	[56]
The Encyclopedia of DNA Elements (ENCODE)	(https://www.encodeproject.org/)	[58]
Gene Expression Omnibus (GeO)	(https://www.ncbi.nlm.nih.gov/geo)	[59]
Gene Ontology (GO)	(http://geneontology.org/)	[60]
Uniprot	(https://www.uniprot.org/)	[61]
DisGeNET	(http://www.disgenet.org/)	[62]
ROADMAP	(http://www.roadmapepigenomics.org/)	[63]
Online Mendelian Inheritance in Man (OMIM)	(https://www.omim.org/)	[64]
Kyoto-Encyclopedia of Genes and Genomes (KEGG pathway)	(https://www.genome.jp/kegg/pathway.html)	[65]

2. Network-based approaches

Various network-based techniques have yet to emerge. Integrative techniques incorporating multi-omic data in networks have been used to uncover susceptibility genes and pathways, particularly in NDs.

2.1. Interconnected gene network

To find and prioritise novel potential susceptibility genes, one strategy employs a cluster of well-characterized disease-associated genes. This technique is based on the model assumption that disease-related genes are commonly involved in comparable biological processes, and so are densely coupled in molecular networks. Like, 31 novel candidate genes related to LOAD were found using a collection of eight confirmed AD genes [66].

2.2. Differential co-expression analysis (DCA)

Differential co-expression analysis (DCA) uses disease nodes or important regulators of biological processes that can be identified using differential co-expression networks. DCA has the benefit of detecting gene regulation patterns of co-expression that may occur in the absence of differential expression and may be missed by typical differential expression analysis [67]. DCA can also detect significant gene association patterns between two sets of phenotypically distinct samples, making it a useful tool for analyzing two or more disorders. APBA2, FYN, RNF219, and SV2A, for example, were identified as possible modulators of LOAD implicated in APP endocytosis and metabolism utilizing DCA [68].

2.3. Weighted gene co-expression network analysis (WGCNA)

WGCNA is a useful method for recognising strongly connected modules in large-scale networks [69]. WGCNA is based on the assumption that highly coexpressed gene modules are usually involved in biological processes that are similar [70, 71]. The development of gene coexpression networks from postmortem LOAD brain tissue showed modules related to microglia signalling cascades, such as TYROBP over expression [31].

2.4. Network-based analysis of genetic associations (NBAGA)

To organise and suggest biological processes and pathways based on disease, a hybrid network technique (network-based analysis of genetic associations (NBAGA)) can be used to assess all the genes affected by CNVs in autism at the same time. The hybrid network was built by examining edges (connectivity) based on shared Gene Ontology annotations, KEGG pathways interaction partners, and co-evolutionary tendencies [72].

2.5. Integrated network approaches

Integrated network techniques that combine numerous data sources could be useful in understanding the biological foundations of Alzheimer's disease. A recent examination of data from GWAS, genome-wide linkage analysis, and gene expression profiling, followed by PPI network analysis, discovered 108 possible Alzheimer's disease susceptibility genes. Some investigations have also revealed extensive information regarding miRNA-132-3p down regulation, which may contribute to AD progression by deregulating mRNA targets in the tau protein network [73].

Due to the extensive clinical overlap with atypical parkinsonian illnesses, proper diagnosis of PD remains difficult. PSP (progressive supranuclear palsy) is a prevalent atypical parkinsonian syndrome that is sometimes misdiagnosed as Parkinson's disease. Using Integrative network analysis, a molecular cluster of 843 possible neighbours was rated and prioritised using well-characterized genes related with PSP. Common molecular networks have been shown to be a source of biomarkers for Parkinson's disease (PD) by establishing links between PD and type 2 diabetes (T2D) [74, 75]. In this sense, system-based techniques have recently been proposed to better comprehend the shared pathways in PD and T2D [76].

Table 3: Analytical tools to visualize biological networks

Tools	Website	Function	Reference
Cytoscape	(https://cytoscape.org)	Integrated network analysis	[77]
Yed	(https://www.yworks.com/products/yed)	Network analysis	[78]
MAGNET	(http://magnet.case.edu/)	Integrated network analysis	[79]
Toppgene	(https://toppgene.cchmc.org/)	Gene prioritization	[80]
INMEX	(http://www.inmex.ca/INMEX/)	Integrated network analysis	[81]
DisGeNET	(http://ibi.imim.es/web/DisGeNET/v01/)	Disease networks	[82]
Network analyst	(http://www.networkanalyst.ca/)	Integrated network analysis	[83]
Gene mania	(http://www.genemania.org/plugin/)	Gene ontology and pathway analysis	[84]
Hefalmp	(http://hefalmp.princeton.edu/)	Disease networks	[85]
Disease connect	(http://disease-connect.org/)	Analysis of disease co morbidities	[86]

3. CONCLUSION

Neurodegenerative diseases results in the progressive degeneration or death of neurons. As it has a substantial impact on global health and no curative treatments are available till date. There are hundreds of neurodegenerative disorders, the majority of which are incurable, including Alzheimer's disease, Amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, Multiple sclerosis, and others. In this review we are highlighting the technological and computational techniques that are applying in the study of neurodegenerative diseases. Some of the molecular objectives that are required in the diagnostic and therapeutic treatments of the NDs such as Differential gene expression analysis, emergence of non-coding RNAs and network building enhancing functional annotations. Some network-based approaches such as DCA, WGCNA and NBAGA etc are developed yet, which are used to identify the susceptibility genes and pathways. Still, new and advance research targets the improvement of more futuristic diagnostic tools (genomic, proteomic biomarkers, and neuro imaging), although precautionary studies are also under way. If all these research endeavor bring to accomplishment in the time ahead.

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5. CONFLICT OF INTEREST

The authors declare no conflict of interest.

6. AUTHOR'S CONTRIBUTION

DK, KSM, ZP, NK, MPT, RV, AS, SK, PRS did intensive research on various 'Bioinformatics approaches using computational tools of neurodegenerative diseases' topics developed; DK, KSM, ZP contributed in writing the manuscript; Scientist MN designed and supervised the present review article and assisted in writing the paper.

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