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Review Article

Biomarkers Unveiling Neurodegeneration: Keys to Progression and Therapeutic Insights

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ABSTRACT

Neurodegenerative diseases constitute a pressing global health challenge, characterized by the gradual loss of neuronal function and structure, leading to cognitive impairment and motor deficits. Biomarkers play a crucial role in understanding the complex pathophysiological pathways of neurodegenerative disorders. By analyzing a variety of recent studies and advancements in the field, we aim to unravel the potential of biomarkers in not only facilitating early diagnosis but also shedding light on disease progression and, consequently, offering critical insights into therapeutic strategies including network pharmacology. These biomarkers cover a wide range of neuroimaging, cerebrospinal fluid, blood-based and genetic markers that help us better understanding of disease etiology and progression. Furthermore, this article explores the dynamic field of biomarker research, including the integration of advanced technologies such as neuroimaging, genomics and proteomics along with the challenges and limitations in the field, including standardization and validation issues, as well as ethical concerns surrounding the use of biomarkers. This review serves as a comprehensive resource for researchers, clinicians and doctors interested in the fight against neurodegenerative diseases. By synthesizing current knowledge on biomarkers, their potential as diagnostic, prognostic and therapeutic tools, ultimately contributing to the development of innovative strategies aimed at mitigating the devastating impact of neurodegeneration can be elucidated.

Keywords: Neurodegenerative Diseases, Biomarkers, Dementia, Cerebrospinal Fluid, Blood-Brain Barrier, Neuroimaging Techniques.

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INTRODUCTION

Neurodegenerative diseases represent a pressing global health concern, exacerbated by an aging population.[1] Neurodegenerative diseases, like Alzheimer's Disease (AD), Parkinson's Disease (PD), Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (ML), Prion Disease (PrD), Frontotemporal Dementia (FTD) and Huntington's Disease (HD), pose a growing global health challenge.[2,3] These conditions have a great impact, gradually decline cognitive and motor abilities from individuals and burdening society.[4] Neurodegenerative diseases affect more than 50 million people around the world and that number is expected to rise significantly in the future. This show how important these conditions are on a global scale.[2] To deal with this growing healthcare problem, we need exact ways to diagnose, predict and treat it. Biomarkers have become essential in the diagnosis and treatment of neurodegenerative disorders. They help us understand how these diseases progress and, importantly, guide the development of effective treatments.[5,6] This review explores the complex nature of neurodegenerative biomarkers, providing a comprehensive overview of their role in disease progression and offering valuable insights into potential treatment strategies. As we delve into this multifaceted topic, we will discuss the significance of biomarkers in the context of neurodegeneration, the various types used in research and clinical practice and how they are developing for early diagnosis and disease monitoring.

Key biomarkers include neuroimaging biomarkers, CSF proteins, blood-based markers and genetic markers, each offering unique insights into the disease mechanisms and progression.[7,8] Blood-based biomarkers are gaining attention due to their less invasive nature and potential for large-scale screening.[9,10] In addition, genetic biomarkers include mutations in specific genes like APP, PSEN1 and MAPT, are important for understanding hereditary forms of neurodegenerative diseases.[11,12] Genetic testing can provide valuable information for risk assessment and early intervention.[13,14]

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Furthermore, we will examine recent advances in biomarker research, including innovative technologies and emerging candidates that hold promise for transforming our understanding of neurodegenerative diseases and aiding the development of targeted therapies. Emerging biomarkers, such as extracellular vesicles and metabolomic profiles, are also showing potential in providing more precise and early detection capabilities.[15-18] Our aim is to provide readers with a comprehensive understanding of biomarkers and their critical function in the field of neurodegeneration. We seek to elucidate the complex mechanisms underlying disease progression and highlight their potential as targets for therapeutic intervention. This investigation not only looked into the complexities of biology and medicine, but it also serves as a light of hope for the millions of people and families affected by neurodegenerative disorders. Together, we strive to unlock the keys to disease progression and usher in a new era of therapeutic insights. By advancing biomarker research and integrating these findings into clinical practice, we aim to improve patient outcomes, enhance Quality of Life (QoL) and ultimately pave the way for the prevention and cure of neurodegenerative diseases.

Role of Biomarkers in Disease Detection

In the rapidly advancing field of medicine, biomarkers have emerged as invaluable tools in understanding and diagnosing diseases.[19] These unique indicators provide essential information about the physiological processes and act as valuable indications in the identification of diseases. Biomarkers, often referred to as biological indicators, play a critical role in the area of medicine by offering vital insights into the physiological processes of the human body. Understanding biomarkers is essential as they serve as powerful clues for disease detection.[20] The significance of biomarkers in disease diagnosis cannot be overstated. They help us detect diseases at earlier stages, sometimes even before symptoms appear. This early detection is a game-changer, as it allows for timely intervention and better treatment outcomes. Biomarkers also play a crucial role in monitoring disease progression and assessing treatment effectiveness.[21] In this comprehensive review article, we will delve deeply into the world of biomarkers. We will explore the diverse types of biomarkers and their wide-ranging applications in neurodegenerative disease. Through this exploration, we aim to elucidate how biomarkers are reshaping the landscape of disease diagnosis, offering the promise of more precise and personalized medical interventions.

Types of biomarkers: proteins, genetic and imaging

Protein Biomarkers

In the domain of neurodegenerative diseases, a variety of protein biomarkers play a crucial role in explaining the complex progression and providing valuable therapeutic insights. These biomarkers are not one-size-fits-all; instead, they are distinct across various neurodegenerative diseases, shedding light on the unique pathophysiological process involved.[22] In AD, the focal point is in the buildup of Amyloid-Beta (Aβ) plaques and tau tangles, which play a crucial role as significant biomarkers. Monitoring their levels provides crucial insights into the disease's advancement, allowing researchers to track progression and explore potential therapeutic interventions.[23] Similarly, in PD, the misfolding and aggregation of Alpha-Synuclein (α-Syn) are central to the pathology. α-Synserves as a pivotal biomarker, offering insights into disease progression and guiding the development of targeted therapies.[24] On the other hand, HD is closely tied to the expansion of the Huntingtin protein (HTT). Biomarkers related to huntingtin aggregation and toxicity is instrumental in monitoring disease progression and devising strategies to mitigate its effects.[25] Likewise, ALS presents the mislocalization and aggregation of TAR DNA-binding Protein 43 (TDP-43) and Fused in Sarcoma (FUS) proteins, which act as key biomarkers. Understanding the complex structure of these proteins is essential for monitoring the progression of the disease and identifying potential therapeutic targets.[26,27] In cases of PrD, abnormal amounts of Prion Protein (PRNP) accumulate in the body. PRNP monitoring is essential for the diagnosis and understanding of the course of this uncommon but catastrophic disorders.[28] Lastly, the Neurofilament Light chain (NfL) protein serves as a versatile biomarker found in the Cerebrospinal Fluid (CSF) and blood. Elevated NfL levels are associated with various neurodegenerative diseases, acting as a general marker of neuroaxonal damage and offering valuable insights into disease progression and potential treatment strategies.[29] In the quest to combat neurodegeneration, these diverse protein biomarkers act as keys, unlocking the secrets of disease progression and offering valuable insights into potential therapeutic avenues. Understanding their roles and interplay is essential for advancing research and ultimately improving the lives of individuals affected by these devastating conditions.

Genetic Biomarkers

In the complex landscape of neurodegenerative diseases, genetic biomarkers serve as crucial navigators, illuminating the path to understanding and intervention. These molecular indicators, each unique to its respective condition, play a significant role in unraveling the mysteries of disease progression and charting the course towards potential therapies.[11] In AD, the spotlight falls on Apolipoprotein E (APOE) gene variants. The APOE ε4 variant elevates the risk of AD, while ε2 appears to offer protection. These genetic cues not only predict susceptibility but also shape therapeutic strategies, as researchers explore ways to counter the influence of APOE-related mechanisms.[30] Shifting our attention to PD, Leucine-Rich Repeat Kinase 2 (LRRK2) gene mutations assume significance. A substantial proportion of familial Parkinson's cases can be attributed to these genetic alterations. Understanding LRRK2's role not only aids in early diagnosis but

also kindles hope for tailored treatments aimed at addressing the underlying genetic biomarkers.[31] In HD, the relentless progression of symptoms is rooted in Huntingtin gene (HTT) mutations. Genetic tests for HTT mutations not only bring diagnostic clarity but also offer insights into disease progression. Researchers are tirelessly working on therapies designed to halt or alleviate the effects of this genetic culprit.[32] In the realm of ALS and FTD, repeat expansions in the Chromosome 9 open reading frame 72 (C9orf72) genes are main. Targeting C9orf72-related mechanisms provides a glimmer of hope for managing these complex diseases, which often share overlapping symptoms.[33] While not previously discussed, PrD find their genetic foundation in the PRNP gene. Genetic variations here play a pivotal role in disease susceptibility and progression, providing vital diagnostic clues and serving as potential targets for therapeutic interventions.[34]

Imaging Biomarkers

Within the diverse spectrum of neurodegenerative diseases, imaging biomarkers emerge as indispensable tools, illuminating the path towards early diagnosis and therapeutic insights. These unique biomarkers, specific to each condition, play pivotal roles in unraveling the complex puzzle of disease progression.[35] Consider AD, where neuroimaging techniques such as Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) play pivotal roles. PET scans, for instance, enable the visualization of amyloid-beta plaques, a hallmark of this condition, while MRI captures structural changes within the brain.These imaging biomarkers enable early detection, tracking disease progression and assessing the efficacy of experimental treatments.[36-39] Similarly, in PD, an array of imaging techniques, including Dopamine Transporter Scan(DaTscan)using Single Photon Emission Computed Tomography (SPECT) and functional MRI (fMRI), unveil vital information. DaTscan SPECT offers insights into dopamine transporter levels, a key diagnostic marker, while fMRI delves into alterations in neural activity, guiding researchers in their quest to develop potential therapeutic interventions.[40,41] Now, consider HD, where MRI and Diffusion Tensor Imaging (DTI) step into the spotlight. These imaging tools capture structural alterations and white matter changes in the brain, yielding essential data that contributes to our understanding of disease progression and the assessment of emerging therapeutic approaches.[42,43] In the case of ALS, a notoriously challenging disease to diagnose and monitor, imaging biomarkers like spinal cord MRI and functional connectivity MRI prove invaluable. These techniques provide glimpses into the disease's impact on the central nervous system, aiding in early detection and the ongoing tracking of progression.[44,45] In PrD, Diffusion-Weighted Magnetic Resonance Imaging (DW-MRI) takes the stage. This technique detects changes in the brain's diffusion of water molecules, a direct consequence of the damage caused by abnormal PRNP. By visualizing these alterations, DW-MRI offers a clear indication of PrD presence and progression.[46,47]

Meanwhile, in the context of FTD, imaging biomarkers like Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) and structural MRI provide critical insights. FDG-PET measures glucose metabolism, revealing reduced uptake in the frontal and temporal lobes, areas typically affected by FTD. This biomarker highlights metabolic changes, aiding in early diagnosis and distinguishing FTD from other dementia.[48,49] In tandem with FDG-PET, structural MRI becomes an essential tool for visualizing atrophy patterns in specific brain regions, notably the frontal and temporal lobes. As FTD advances, these areas tend to shrink, a process quantified by structural MRI. This imaging biomarker offers valuable information for diagnosis and ongoing monitoring.[50]

Key Biomarkers in ADProgression

Biomarkers play a crucial role in advancing our understanding of the progression of AD as well as providing multifaceted insights into the complicated nature of neurodegenerative disorders.[51,52] Amyloid Beta and Tau proteins are widely recognized as the primary biomarkers associated with cognitive impairment. Aβis widely recognized for its tendency to aggregate into plaques, whereas tau proteins are responsible for the formation of Neurofibrillary Tangles (NFT), both of which are prominent pathological hallmarks associated with AD.[53,54] Nowadays, researchers have harnessed these biomarkers for diagnostic and monitoring purposes.[55-58] Elevated levels of Aβin CSF have been correlated with the presence and progression of AD, while tau protein patterns in neuroimaging, especially through PET scans, provide a non-invasive means to visualize tau pathology in human brains, aiding in disease staging.[59,60] In addition to these protein indicators, the utilization of Cerebrospinal Fluid (CSF) markers has significantly enhanced our comprehension.[8,48] The indicators comprise a range of factors, such as the APOE genotype and markers associated with synaptic dysfunction. In particular, genetic factor has shed light on susceptibility and risk factors associated with AD.[61,62]

In the realm of neuroimaging, advanced techniques have revolutionized our ability to study AD *in vivo*.[63,64] PET scans using specialized tracers have the capability to accurately visualize Aβ plaques and NFT.[65] Similarly, fMRI has the capacity to unveil changes in cerebral activity and connection, thereby offering valuable insights into the underlying mechanisms of diseases.[66] Collectively, these diverse biomarkers hold significant promise in transforming AD research and clinical practice. They facilitate early diagnosis, allowing for interventions at a stage where treatments may be more effective.[67-68] Moreover, biomarkers aid in patient stratification for clinical trials and provide objective measures to assess treatment responses.[69] As our understanding of AD continues to deepen, the integration of these biomarkers into clinical care and drug development is paramount in our pursuit of more effective therapies for neurodegenerative disease.[70]

Crucial Biomarkers in PDProgression

Biomarkers play a pivotal role in PD progression and it advancing our understanding of the disease's pathophysiology. PD is characterized by the progressive degeneration of dopaminergic neurons in the brain, leading to motor symptoms like tremors, bradykinesia and rigidity.[71] Biomarkers serve as measurable indicators of the underlying molecular and cellular changes that occur during PD. α-Syn is a protein closely associated with the pathophysiology of PD. In PD, α-Syn aggregates abnormally along with forming Lewy bodies which are pathological hallmarks of the disease. These aggregates are believed to contribute to neurodegeneration. Biomarkers research has focused on detecting and quantifying α-Syn levels in various bodily fluids and tissues such as CSF and skin. The presence and quantify of α-Syn in this type of sample can provide valuable insights into disease progression and severity.[72-74] Furthermore, dopaminergic neurons in the substantia nigra are significantly affected in PD, resulting in a depletion of dopamine levels in the brain. Advanced neuroimaging techniques, including DaTscan and PET scans, allow for the visualization and measurement of dopamine activity in the brain.[75,76] By monitoring changes in dopaminergic function, clinicians can easily assess the extent of dopaminergic neuron loss, which correlates with disease severity.[77] This imaging technique provides clear insights into the disease progression as well as uses as aids in diagnosing PD.[78]

While most PD cases appear without a clear cause, some people have genes that make them more likely to develop the disease. Certain genetic changes, like those in genes called LRRK2 and Glucocerebrosidase (GBA), are associated with a higher risk of PD. Mutations or variations of these genes can increase an individual's susceptibility to PD.[79] Changes in genes can affect the functioning of proteins and processes in the brain, leading to the gradual degeneration of dopamine-producing neurons and the characteristics symptoms of PD such as tremors and movement difficulties. However, these genetic markers provide a direct link between genetics and pathophysiology of PD.[80,81] Studying the genetic profiles of individuals with PD helps researchers uncover the molecular mechanisms underlying the disease and lead to the development of targeted therapies. Additionally, genetic biomarkers can identify individuals at higher risk, allowing for early intervention and personalized treatment strategies.[82-84]

Primary Biomarkers in ALSProgression

In the quest to understand and combat the progression of ALS, biomarkers have emerged as critical guides. Within the complex pathophysiology of ALS, biomarkers such as TDP-43 and Superoxide Dismutase 1 (SOD1) have taken center stage, offering insights into the mechanisms of disease. TDP-43 is a protein found in the nucleus of cells, take center stage due to its abnormal aggregation in the neurons of ALS patients. This aggregation is closely linked to the pathophysiology of ALS. When TDP-43 accumulates in motor neurons, it disrupts normal cellular processes, leading to neuronal dysfunction and ultimately causes the cell death. This cascade of events contributes significantly to the progression of ALS.[85] On the other hand, SOD1 represents genetic biomarker and mutations in the SOD1 genes are known to cause a rare form of familial ALS. These mutations lead to the production of faulty SOD1 enzymes, which play role in protecting cells from oxidative stress.[86] However, in ALS, mutant SOD1 proteins become toxic and damage motor neurons, setting the stage for the progression of disease. Electrophysiological markers, another facet of ALS biomarkers, provide valuable real-time insights into the functioning of motor neurons.[87] These markers often assessed through techniques like Electromyography (EMG) and also help clinicians monitor the loss of motor neuron function, a hallmark of ALS. Such monitoring aids in early diagnosis and tracking disease progression.[88,89] Beyond these markers, genetic factors illuminated the genetic landscape of ALS. Various gene mutations, including C9orf72 and FUS, have been identified, linking specific genetic alterations to ALS susceptibility. Together, these biomarkers expand our knowledge about ALS pathophysiology and offering potential avenues for therapeutic intervention along with the exploration for a cure.[90]

Core Biomarkers in HD Progression

In the ongoing quest to comprehend and address HD, three core biomarkers take the spotlight. Firstly, Mutant HTT (mHTT) Protein which produced due to the genetic mutation and this aberrant protein aggregates within the brain cells, particularly in the striatum leading to cellular dysfunction and neuronal death.[91,92] Biomarker has centered on detecting and quantifying mHTT levels in various tissues such as CSF and blood, offering a direct insight into the disease's progression. Advanced neuroimaging techniques, including MRI and PET scans have unveiled structural and functional changes in the brains of individuals of HD. These neuroimaging markers provide invaluable insights into the degeneration of specific bran regions, such as the striatum and cortex, offering a visual representation of disease progression.[93] Moreover, clinical assessment measuring cognitive and motor function serves as essential biomarkers in HD. These assessments help healthcare professionals track the gradual decline in motor control, cognitive abilities and psychiatric symptoms experienced by individuals with HD. Monitoring these changes over time is crucial for understanding disease progression and tailoring care.[94] As a result, biomarkers provide clear insights into the underlying molecular process, structural brain alterations and clinical manifestations, ultimately guiding efforts to develop effective treatments and interventions for people affected by HD.

Central Biomarkers in PrD Progression

PrD are a group of rare and fatal neurodegenerative disorders characterized by the accumulation of misfolded PRNP in the

CNS.[95] These diseases, including Creutzfeldt-Jakob disease and variant Creutzfeldt-Jakob disease, have no effective treatments, making early diagnosis essential.[86] Central biomarkers have emerged as promising tools for understanding the pathogenesis and monitoring the progression of PrD. One of the central biomarkers associated with PrD is the detection of abnormal PRNP in CSF and brain tissues.[96] The accumulation of PRNP is a hallmark of PrD and serves as a specific diagnostic indicator. Moreover, the presence of PRNP in different regions of the brain correlates with the clinical symptoms and disease progression which reflecting the spread of prion pathology. Furthermore, CSF analysis also provides insights into PrD progression.[97] Elevated levels of total tau proteins and 14-3-3 protein in CSF is often observed in prion-infected individuals. These biomarkers correlate with neuronal damage and help distinguish PrD from other neurodegenerative disease. Additionally, changes in the level of biomarkers in CSF over time provide valuable information about the progression of disease.[98]

In addition, advanced neuroimaging techniques such as MRI and PET have been used as instrumental tools in studying PrD biomarkers. These imaging modalities can reveal structural and functional changes associates with disease progression, including atrophy disease progression and alterations in glucose metabolism.[99] However, genetic biomarkers are also relevant in PrD diseases, as specific mutations in PRNP gene can predispose individuals to these disorders. Genetic testing for PRNP mutations can aid in early identification of individuals at risk, allowing for timely surveillance and potential interventions.[100]

Pivotal Biomarkers in FTD-Dementia Progression

FTD-Dementia is challenging neurodegenerative disorder marked by progressive cognitive and behavioral impairments.[101] The identification and understanding of pivotal biomarkers in FTD have become essential for early diagnosis and tracking disease progression. In FTD, one prominent biomarker is the accumulation of abnormal proteins, such as tau and TDP-43 in the frontal and temporal lobes of the brain.[102] In particular, tau pathology strongly is associated with FTD and detected through CSF analysis and neuroimaging. Increase levels of tau in the CSF correlate with cognitive decline and differentiate FTD from other forms of dementia.[103] Likewise, another vital biomarker in FTD is the Progranulin (GRN) gene. Mutations in GRN gene are known are known to cause a familial form of FTD. Genetic testing can identify individuals at risk and help to understand the genetic basis of the disease. Additionally, the presence of GRN mutations can be indicative of specific disease subtypes and may influence disease progression.[104,105] Connecting with the earlier discussion, advanced neuroimaging techniques such as MRI and PET scans provide valuable insights into FTD biomarkers. They can visualize structural changes in the brain, including atrophy of the frontal and temporal lobes.[106-108] Moreover, functional imaging can reveal alterations in brain connectivity, aiding in the understanding of FTD's impact on neural networks.[109,110] However, metabolic biomarkers such as changes in glucose metabolism observed through PET scans are also linked with FTD. These biomarkers can reflect disease severity and progression, offering clinician's valuable information for patient management.[111] As research in this field continues to evolve, these biomarkers hold the potential to enhance our ability to diagnose FTD early and develop targeted therapies to alleviate its devastating impact on patients and their families.[112]

Fundamental Biomarkers in Multiple Sclerosis Progression

MS is a complex autoimmune disease that affects the central CNS and several biomarkers play critical roles in its diagnosis and disease progression tracking.[113] Myelin Basic Protein (MBP) reflects myelin damage, with elevated levels indicating active disease and correlating with symptom severity.[114] Similarly, Oligoclonal Bands (OCBs) are characteristics of MS and signify immune system activity within the CNS, aiding in diagnosis and providing insights into disease aggressiveness.[115] In addition, NfL serves as a promising marker for ongoing nerve damage, predicting future disability and indicating treatment response.[116] Moreover, Myelin Oligodendrocyte Glycoprotein (MOG) antibodies, though not universal in MS, signify distinct subsets of the disease.[117] Recently, several advanced technologies are revolutionizing the landscape of MS by enhancing diagnosis, patient care and research. MRI with specialized techniques like DTI and fMRI provides detailed insights into brain lesions, atrophy and neural connectivity changes, aiding in diagnosis and tracking disease progression.[22,118-120] CSF analysis, tough invasive, remains valuable for assessing biomarkers like OCBs and NfL levels.[109,110] Conversely, non-invasive Optical Coherence Tomography (OCT) measures retinal nerve fiber layer thickness, reflecting axonal damage.[118,121,122] On the other hand, advance blood tests and proteomics are being explored to identify specific biomarkers indicative of MS activity.[123,124] Furthermore, artificial intelligence and machine learning algorithms are increasingly used to analyze complex data sets, enhancing the accuracy of diagnosis and predicting disease progression.[125,126] These recent technological advances are invaluable in improving our understanding of MS and guiding more precise treatment strategies for individual living with this condition.

Correlation between Inflammatory Biomarkers and Neurodegenerative Diseases

The link between neuroinflammation biomarkers and neurodegenerative diseases is a topic significant interest in the field of neuroscience and medicine. Neuroinflammation refers to the inflammation that occurs specifically within the CNS. Unlike systemic inflammation, this is typically a response to infections or injuries elsewhere in the body. Chronic inflammation within the brain can lead to neuronal damage

and exacerbate disease progression.[127,128] Neuroinflammation involves immune responses within the brain and spinal cord, primarily mediated by microglia resistant immune cells of the CNS, as well as astrocytes and the release of inflammatory cytokinessuch as interleukin-1β, Tumor Necrosis Factor-alpha (TNF-alpha) and Interleukin-6(IL-6).[129,130] These inflammatory markers, along with reactive oxygen species and nitric oxide contribute to neuronal damage by promoting oxidative stress and inflammation within the brain.[131] Moreover, activated microglia, a hallmark of neuroinflammation, release pro-inflammatory cytokines, further exacerbating neuronal dysfunction and cell death, common characteristics of neurodegenerative diseases.[129] The inflammation process can also disrupt the BBB, enabling immune cells and inflammatory molecules to enter into the brain and promote the inflammatory responses.[131] This, in turn, impacts the accumulation of pathological proteins like Aβ and α-Syn, seen in conditions such as AD and PD, while also leading to synaptic dysfunction, contributing to cognitive deficits.[132] Recognizing the role of these inflammatory markers is crucial for early diagnosis, as elevated levels in CSF and blood serves as indicators, potentially allowing for timely interventions and the development of therapeutic targeting neuroinflammation to mitigate disease progression.[133,134] Interconnection Between Pathological Mechanisms in Neurodegenerative Diseases: Mitochondrial Dysfunction, Oxidative Stress and Inflammation is depicted in Figure 1.

Emerging Biomarkers for Early Diagnosis

Emerging biomarkers are becoming increasingly vital in the early diagnosis of neurodegenerative diseases, including AD, PD, HD, ALS, PrD and FTD-dementia. These biomarkers offer non-invasive methods to detect these conditions at their initial stages, providing opportunities for timely intervention and improved patient's outcomes.[135] One prominent category of emerging biomarkers focused on blood-based indicators. Analyzing blood components, such as proteins, metabolites and genetic material, has shown promise.[136] For example, increase levels of Aβ and tau proteins in the blood are associated with AD, making them potentially early indicators.[137] Similarly, the measurement of NfL in the bloodstream has shown promise in diagnosing diseases like ALS and MS.[138] However, another significant area of interest involves neuroinflammation and glial biomarkers. Neuroinflammaion plays a pivotal role in the progression of neurodegenerative diseases. Biomarkers associated with this process, such as glial fibrillary acidic protein, can indicate astrocyte activation and neuroinflammation. Additionally, certain

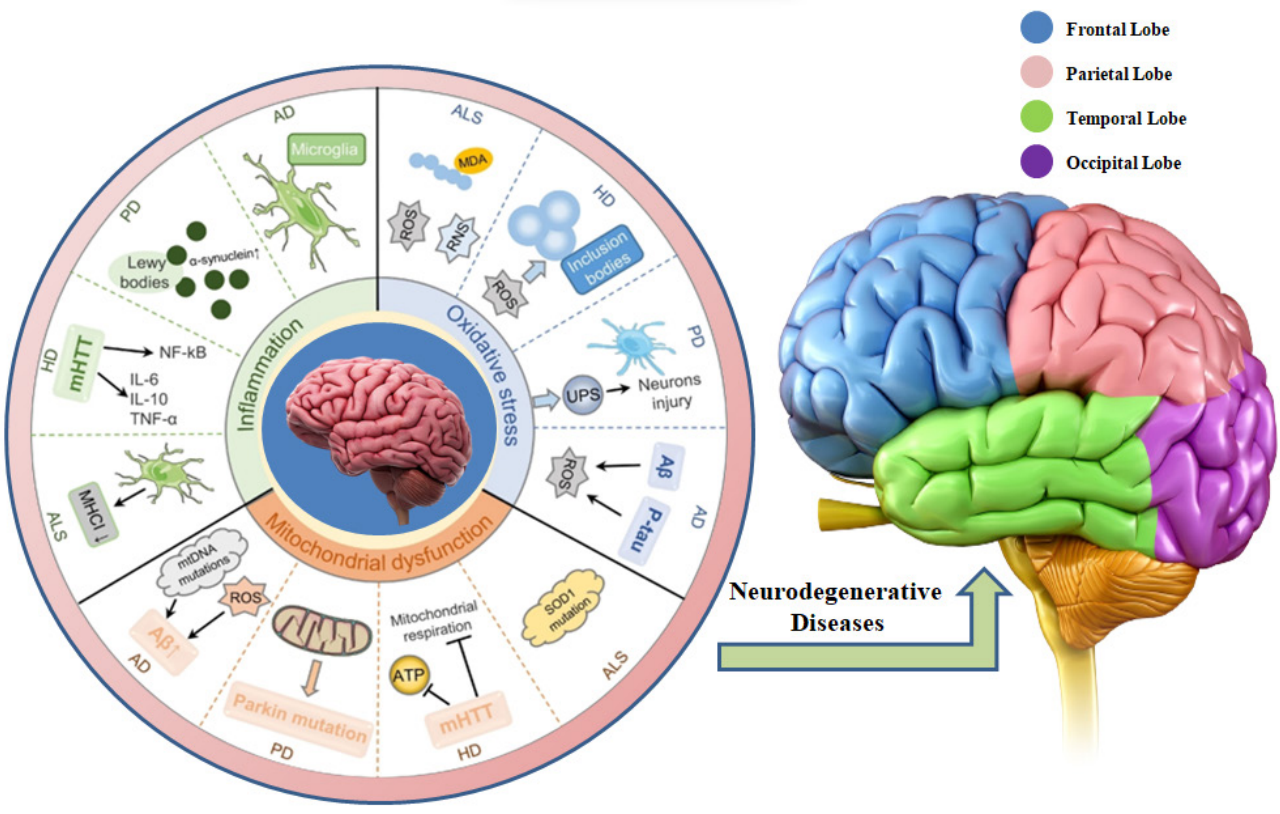

Figure 1: Interconnection Between Pathological Mechanisms in Neurodegenerative Diseases: Mitochondrial Dysfunction, Oxidative Stress, and Inflammation.

This figure illustrates the intricate connection between neuroinflammation and a group of neurodegenerative diseases. It highlights the central role of neuroinflammation as a common pathological feature in these conditions, with inflammatory processes contributing to the progression and exacerbation of these devastating diseases. The pathogenesis of aging-related neurodegenerative diseases involves key mechanisms like mitochondrial dysfunction, oxidative stress, and neuroinflammation which lead to the progression of neurodegenerative diseases.

cytokines and chemokine's, IL-6, TNF-alpha, have been linked to neuroinflammation in various neurodegenerative conditions.[139,140] Furthermore, liquid biopsies represent a cutting-edge approach to diagnosis. These tests involve the analysis of biofluids, such as blood, CSF, or even saliva. Liquid biopsy methods, like the analysis of cell-free DNA in the bloodstream, may reveal genetic mutations associated neurodegenerative diseases. Extracellular vesicles, including exosomes, carry biomolecules reflective of disease status, making them valuable diagnostic tools.[141,142]

Therapeutic Implication of Biomarkers Research

The field of biomarker research in neurodegenerative diseases presents promising therapeutic implications that are pivotal for advancing diagnosis, treatment and patient care. Advanced Technology Applications in the Diagnosis, Treatment and Monitoring of Various Neurodegenerative Disease is depicted in Figure 2. One crucial aspect is the advent of personalized medicine approaches facilitated by biomarkers. These biomarkers allow clinicians to customize treatment plans according to an individual's unique biomarker profile, enabling a departure from the conventional one-size-fits-all approach and yielding optimized treatment outcomes.[143] For instance, in AD, biomarkers like Aβ and tau protein levels in CSF or blood can assist in early diagnosis and prognosis, guiding tailored interventions based on disease stage, encompassing lifestyle modifications, cognitive training, or pharmacological therapies.[59,143] Biomarker research

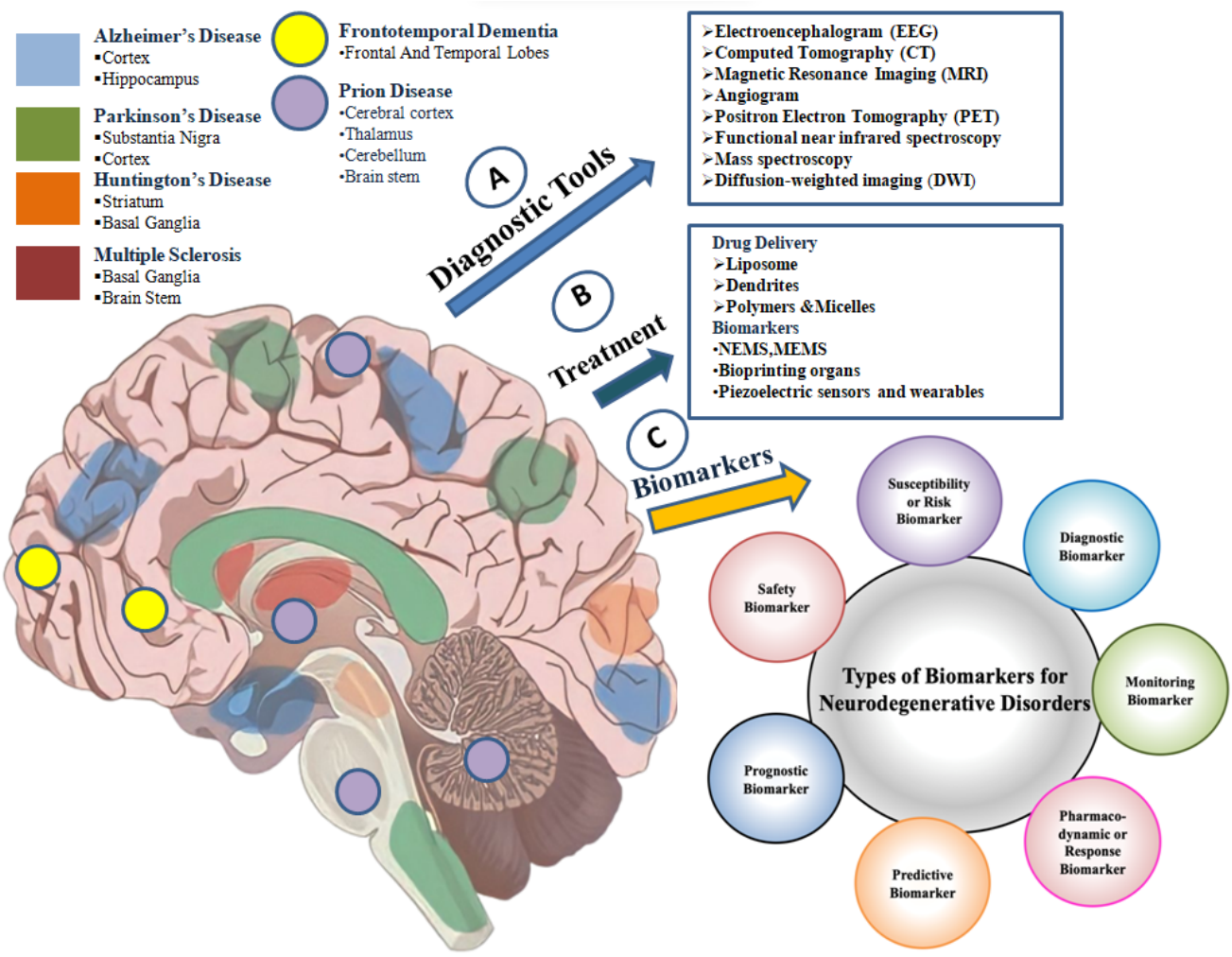

Figure 2: Advanced Technology Applications in the Diagnosis, Treatment, and Monitoring of Various Neurodegenerative Disease.

A) Schematic overview of the review, with an emphasis on the use of 5G technology, artificial intelligence, nanotechnology, self-powered wearable's, and micro electromechanical systems, then the common brain diseases, such as Alzheimer's, Parkinson's, Huntington's, Multiple Sclerosis, Frontotemporal Dementia, Prion Disease, brain infections, brain cancer, and strokes, as well as the advancements in diagnostic tools and treatment approaches. B) Illustration of various platforms based on nanoparticles and their functions in neuroscience applications. In order to examine their potential uses for the diagnosis, treatment, and monitoring of a number of neurological illnesses, these nanoparticles have been widely used in neuroscience research. C) Diagnostic biomarkers are used as a diagnostic tool to find out if a neurodegenerative disorder or one of its subtypes is present. Monitoring biomarkers are used to track the prognosis of a particular neurodegenerative illness or the response to an intervention. The progression of the treatment is determined by pharmacodynamics or response biomarkers, which are also a potential tool in clinical practice for patient management. Risk or Susceptibility Biomarkers are utilized in clinical practice to build a preventive plan and assess the likelihood of getting a particular neurodegenerative disease.

also greatly streamlines drug development and clinical trials in neurodegenerative diseases. Identifying reliable biomarkers for disease progression and therapeutic response leads to more efficient trials, quicker assessment of potential drug candidates and heightened success rates in clinical development.[144] For example, in PD, biomarkers like dopamine transporter imaging or α-Syn levels are employed to monitor disease progression and evaluate experimental treatment efficacy, offering objective measures that expedite the identification of promising drugs and reduce trial durations.[72,73] Furthermore, biomarkers provide a means to continually monitor treatment effectiveness, allowing timely adjustments to treatment plans for improved patient outcomes.[145] In MS, biomarkers like CSF OCBs or NfL levels help clinicians assess the response to disease-modifying therapies, ensuring that patients receive the most suitable treatments, preventing disease relapses and mitigating disability progression.[146] In sum, neurodegenerative disease biomarker research holds transformative therapeutic potential, from enhancing treatment precision through personalized medicine to expediting drug development and clinical trials and facilitating real-time treatment efficacy monitoring, promising a future where these diseases are not just manageable but preventable and treatable, providing hope and improved care for patients and their families.[147]

Network Pharmacology Approach in Neurodegenerative Diseases

In recent years, the field of network pharmacology has emerged as a powerful tool in understanding the complex molecular mechanisms underlying various diseases, including neurodegenerative disorders such as AD, PD, HD, PrD, ALS, MS and FTD-dementia. This innovative approach involves the systemic analysis of genetic markers and their interactions within intricate pathways associated with these conditions. By employing network pharmacology techniques, researchers aim to unravel the intricate web of genetic markers that contribute to the pathogenesis of this neurodegenerative diseases.[148] This methodology integrates information from diverse biological databases, allowing scientists to construct comprehensive networks that highlight the relationships between genes, proteins and signaling pathway involved in disease progression. One of the key advantages of network pharmacology is its ability to reveal the interconnectedness of these diseases at a molecular disease at a molecular level. It helps identify hub genes or a central player that exert significant influence over multiple neurodegenerative pathways, offering valuable insights into potential therapeutic targets.[149] Network Pharmacology of the Most Common Neurodegenerative Disease Genesis depicted in Figure 3. Additionally, this approach aids in the discovery of commonalities and differing among various neurodegenerative diseases, paving the way for the development of more targeted and personalized treatment strategies.[150]

Furthermore, networks pharmacology employs high-throughput omics data, such as genomics, transcriptomics and proteomics, to construct comprehensive gene networks associated with each neurodegenerative disease. Through advanced computational algorithms and statistical analyses, researchers can identify hub genes within these networks. Remarkably, it becomes evident that many hub genes are shared among different neurodegenerative diseases. This shared involvement of hub genes reflects common biological pathways and molecular mechanisms that underlie these conditions.[151] GO Results of Three Ontologies about Biological Process (BP), Cellular Component (CC) and Molecular Function (MF) is depicted in Figure 4. However, hub genes are not isolated entities; they participate in intricate molecular crosstalk. They often regulate common pathways involved in processes like protein aggregation, oxidative stress, inflammation and neuronal cell death- all hallmarks of neurodegeneration. Through their interactions and regulatory functions, hub genes can perpetuate or modulate disease-associated processes across various neurodegenerative diseases.[152] In addition, understanding the interconnectedness of hub genes is invaluable for drug discovery and therapeutic development. Identifying hub genes that are central to multiple neurodegenerative diseases offers promising targets for intervention. Pharmaceutical companies can develop drugs that specifically target these hubs, potentially providing treatments that transcend traditional disease boundaries.[153] Moreover, network pharmacology not only reveals commonalities but also highlights disease-specific differences. By examining how hub genes differ in their connections and activities across various neurodegenerative diseases, researchers can tailor therapeutic approaches to the unique genetic signatures of individual patients. This personalized medicine approach holds tremendous potential for improving treatments outcomes.[154] Overall, the application of neurodegenerative diseases holds great promise in advancing our understanding of the underlying genetic factor and their interactions.[149] This knowledge enhances our comprehension of disease and also facilitates the discovery of novel therapeutic interventions, ultimately bringing us closer to effective treatments for these devastating neurological conditions.[150] KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway analysis is depicted in Figure 5.

Clinical Advancements in Biomarkers for Neurodegeneration

Deep-learning neural networks were utilized by Zhang, Ghose, *et al.* at Oxford University to determine blood proteins that could predict the Amyloid, Tau and Neurodegeneration (AT[N]) pathologies that are currently often utilized as biomarkers in AD. After evaluating the brain's AT[N] status and comparing it to relevant blood biomarkers, they found that proteins in five clusters linked to AD could act as stand-in blood biomarkers for AD.[155] In a similar vein, Chen *et al.* at Taiwan's MacKay Memorial Hospital examined the connection between Motoric Cognitive

Rank	Name	Score
1	APOE	6
2	MAPT	5
2	PRNP	5
2	HTT	5
2	SNCA	5
2	C9orf72	5
7	HLA-DRB1	1

Figure 3a

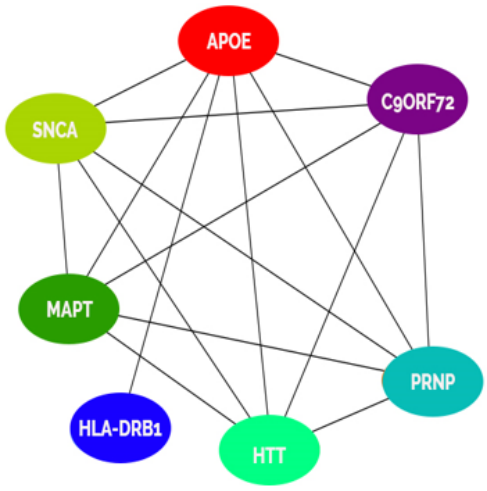

Figure 3b

Figure 3: Network Pharmacology of the Most Common Neurodegenerative Disease Genes.

Genes that have many connections with other genes are termed "hub genes" in gene a network, which usually plays an essential role in gene regulation and biological processes. A high-degree node, or hub, is the core component of any kind of network. When compared to other nodes in the network, hubs have an extremely high link density. If the number of connections between the hubs matches what would be predicted by chance, this network is referred to as Neutral Network. When hubs exhibit a tendency to connect with other hubs while avoiding links with nodes of low degree, the network can be described as an Assortative network. Because the hubs form a core group that is more resilient to hub removal, this network is comparatively resistant to attacks. When hubs refrain from connecting to one another while establishing links with nodes of lower degree, the network in question is commonly referred to as a Disassortative Network. In Figure 3b, APOE which acts as a hub gene in this network moreover this all genes are responsible for most common neurodegenerative diseases. On the other hand, the score means of the Top 7 important genes, APOE is the most highly important gene because it interacts with the other 6 genes rather than other genes which are shown in Figure 3a. In this way, the most important gene will be selected. APOE: Apolipoprotein E; SNCA: Synuclein Alpha; MAPT: Microtubule Associated Protein Tau; HLA-DRB1: Human leukocyte antigen class II histocompatibility D related beta chain; HTT: Huntingtin; PRNP: Prion Protein; C9orf72: Chromosome 9 open reading frame 72.

Risk (MCR) syndrome cognition and blood-based biomarkers of AD. Aβ42 and total tau levels were tested in the plasma and it was discovered that the MCR and AD groups had considerably greater plasma tau levels than the group with normal cognition. These findings suggest that tau levels may be connected to cognitive performance in MCR and that MCR and AD may have similar underlying pathologies.[156] In the meantime, a study conducted by Parvizi *et al.* at the Medical University of Vienna, Austria, investigated the possibility of using Glial Fibrillary Acidic Protein (GFAP) and blood Neurofilament Light chain (NfL) to identify early neuropathological alterations in AD.[157] According to their findings, amyloid positive may be predicted and AD can be distinguished from healthy controls using a panel that combines plasma NfL and GFAP with established AD risk variables.

Using functional enrichment analysis, Heng *et al.* at the Second Affiliated Hospital of Soochow University in China investigated the genetic connection between PD and osteoarthritis. They discovered 71 similar genes affecting both diseases by using bioinformatics techniques and Gene Expression Omnibus database datasets. These genes were prominent in pathways such nucleocytoplasmic transport, mitochondrial translation, antigen processing and presentation and the mRNA surveillance pathway. Their research revealed that multiple immune cell types may be linked to the pathophysiology of both PD and osteoarthritis and that the gene WDR43 may be helpful in detecting both conditions. In order to determine if patients with Multiple System Atrophy (MSA) had aberrantα-syn accumulation in their oral mucosa, Zheng and colleagues at Beijing Tiantan Hospital in China.[158]

Challenges and Future Directions in Biomarkers Studies

Biomarkers studies in neurodegenerative diseases hold immense promise but also face significant challenges that must be addressed for continued progresses in research and clinical applications.[52] In that case, ethical considerations are paramount in biomarker research, particularly in the context of neurodegenerative diseases. The collection and use of biological samples, such as CSF or genetic material, raise concerns about patient consent, privacy and data security. Informed consent processes must be robust and adaptable to account for potential cognitive impairments in patients, especially in advance stages of these diseases. Additionally, ensuring the equitable distribution of benefits and the avoidance of stigmatization related to biomarker findings is crucial. Striking a balance between advancing research and respecting ethical principles remains

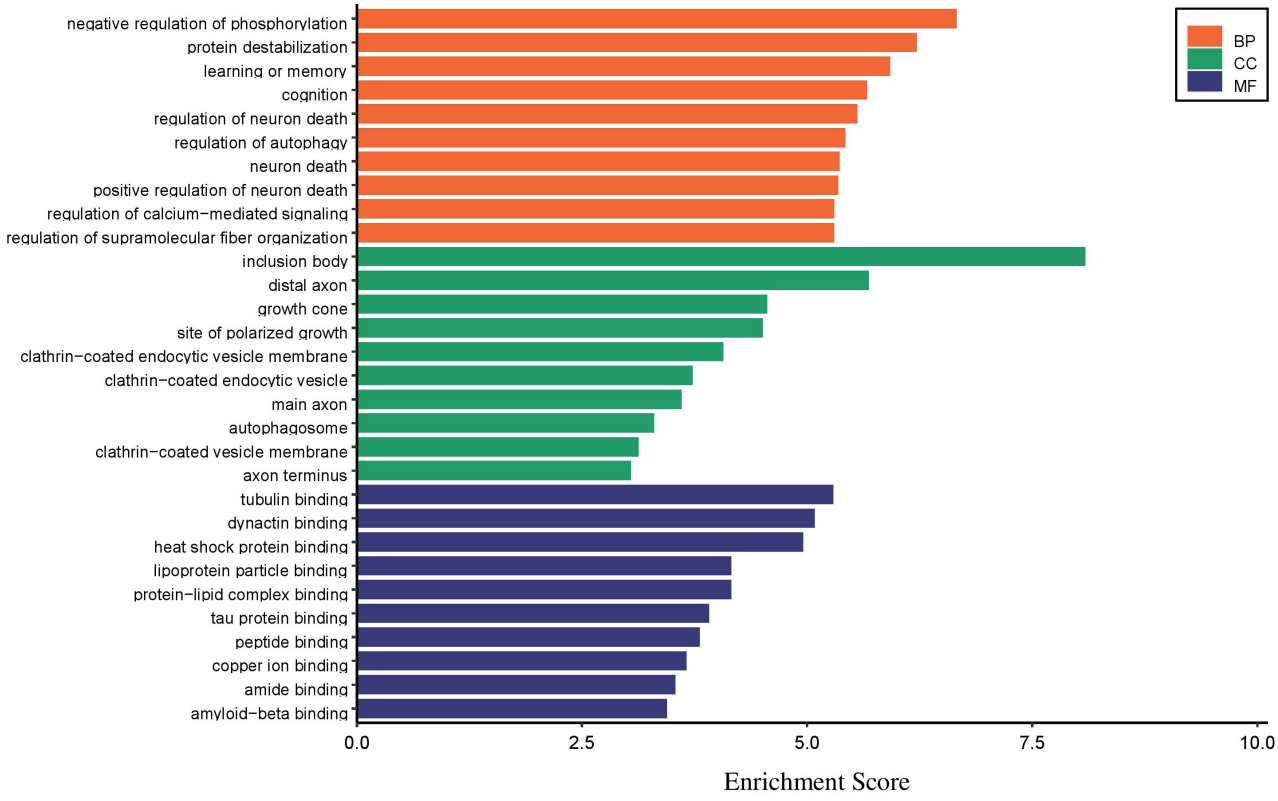

Figure 4: GO Results of Three Ontologies.

The enriched analysis method offers a means to categorize individual genes or molecules based on their respective functional roles. Genes or substances with similar functions are grouped together to save workload and link functions to phenotypes. Enrichment analyses, such as those conducted for Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and Gene Set Enrichment Analysis (GSEA), are commonly utilized in research. The main aim of GO functional annotation is to identify correlations between a specific set of genes and their corresponding functional activities. Gene Ontology is an online database divided into three categories-Biological Process (BP), Cellular Component (CC), and Molecular Function (MF)-that describes the roles that genes and their products play in living organisms. Annotating gene sets to specific entries (terms) within these three categories using the right approaches can provide light on the gene set's function.

an ongoing challenge field.[159,160] Similarly, standardization and reproducibility are essential challenges in biomarkers studies across neurodegenerative diseases. Variability in data collection, assay protocols and data analysis can lead to inconsistent results, hindering the reliability of biomarkers. Establishing standardized procedures and guidelines for sample handling, assay methodologies and data interpretation is imperative. Collaborative across multiple centers is essential for building confidence in the utility of biomarkers for diagnosis, prognosis and treatment monitoring.[161,162] Apart from this, advancements in technology are both a challenge and an opportunity in biomarker research. On one hand, emerging technologies, such as high-resolution imaging, single-cell sequencing and proteomics, offer unprecedented insights into the molecular and cellular changes associated with neurodegenerative diseases. These technologies enable the discovery of novel biomarkers with high sensitivity and specificity.[163] However, the rapid evolution of technology presents challenges related to data integration, analysis and the need for continuously updated methodologies. Additionally, the high cost of some advance technologies may limit their accessibility, emphasizing the importance of equitable access to cutting edge tools.[164,165]

DISCUSSION

The discovery and utilization of biomarkers in the context of neurodegenerative diseases have emerged as a promising avenue for understanding disease progression and developing therapeutic strategies.[5,6] In this review, we delve into the significance of biomarker in neurodegeneration research, their implications for disease progression and the insights they offer for potential treatments. Initially, biomarkers have played a pivotal role in elucidating the intricate pathways and mechanisms underlying neurodegenerative diseases such as AD, PD, HD, ALS, MS and FTD-dementia. By identifying specific diseases, researchers have gained a deeper understanding of their pathophysiology.[166] Furthermore, biomarkers have proven invaluable in tracking disease progression. Longitudinal studies utilizing biomarkers have allowed for the identification of disease stages, enabling early diagnosis and the monitoring of disease evolution over time. This early detection not only improves patient outcomes

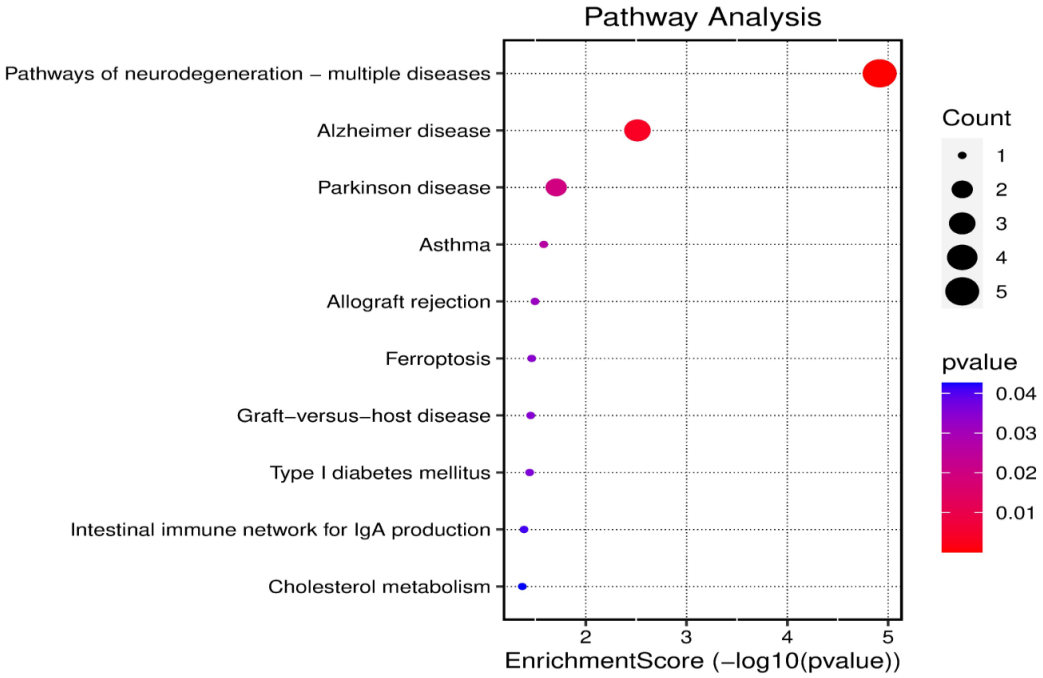

Figure 5: KEGG Enrichment Result.

The x-axis represents the enrichment score in log value. Calculate a p-value representing the probability that the enriched numbers of counts could have resulted from randomly distributing this GO term between the tested set and the reference set. In this plot, the size of each bubble corresponds to the number of genes associated with the pathway. The circle color indicates the significant level with the adjusted p-value <0.05. Larger bubbles signify a higher number of genes enriched in that pathway. The color of the bubbles represents the significance of the p-value, with darker colors (red) indicating a smaller -log10 (p-value) and thus a more significant enrichment. In KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway analysis, the most significantly enriched pathways included the Pathways of neurodegeneration-multiple diseases pathway, Alzheimer's disease, and Parkinson's disease.

but also opens doors to interventions that could potentially slow or decrease disease progression.[167]

In terms of therapeutic insights, biomarker offers a two-fold advantage. Firstly, they serve as objective measures of treatment efficacy. Clinical trials can incorporate biomarkers assessments to provide quantitative data on the impact of experimental therapies, expediting the development of effective drugs.[168] Secondly, biomarkers guide the development of precision medicine approaches. Tailoring treatments based on individual's biomarker profile holds promise of enhancing therapeutic outcomes while minimizing adverse effects.[14] Nonetheless, the utility of biomarkers in neurodegeneration research does come with challenges and limitations. Variability in biomarker expression among individuals, the need for standardized protocols and the ethical considerations surrounding their use are notable hurdles.[169] Moreover, the dynamic nature of neurodegenerative diseases raises questions about the stability and predictive values of certain biomarkers.[170] While challenges remain, ongoing research endeavors to the quest for effective treatments and improve quality of life for individuals affected by neurodegenerative diseases.

CONCLUSION

In conclusion, the exploration of biomarkers in the context of neurodegenerative diseases represents a critical juncture in the field of neuroscience and clinical medicine. The journey of unraveling the secrets of neurodegeneration has been significantly accelerated by these molecular biomarkers. The impact of biomarkers in this domain is multifaceted, with profound implications for research, clinical practice and the development of novel therapeutics. Biomarkers have ushered in a new era of understanding, allowing researchers to dissect the intricate mechanisms driving neurodegeneration diseases with unprecedented precision. They have offered crucial insights into the heterogeneity of these disorders, revealing distinct subtypes and pathological pathways. This knowledge, in turns, guides the development of targeted interventions, moving us closer to the dream of personalized medicine for neurodegeneration. Moreover, the role of biomarkers in disease monitoring cannot be overstated. They provide clinicians with the tools to diagnose neurodegenerative conditions at their early stages, often before overt clinical symptoms manifest. This early detection aids in the optimization of clinical trial designs, expediting the evaluation therapeutics. The promise of biomarkers extends to the therapeutic realm as well. They serve as objective measures of treatment

efficacy, facilitating the identification of effective drug candidates and the monitoring of their impact. The ability to stratify patients on their biomarker profile offers hope for more successful and personalized interventions, addressing the variability in disease progression and treatment response observed in clinical practice. In closing, biomarkers have illuminated the path forward in our quest to unlock the mysteries of neurodegeneration. They stand as beacons of hope, guiding researchers, clinicians and patients alike toward a future where these devastating diseases are better understood, diagnosed earlier and treated more effectively.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AD: Alzheimer's Disease; **PD:** Parkinson's Disease; **ALS:** Amyotrophic Lateral Sclerosis; **ML:** Multiple Sclerosis; **PrD:** Prion Disease; **FTD:** Frontotemporal Dementia; **HD:** Huntington's Disease; **Aβ:** Amyloid-Beta; **α-Syn:** Alpha-Synuclein; **HTT:** Huntingtin Protein;**TDP-43:** TAR DNA-binding protein **43;FUS:** Fused in Sarcoma; **PRNP:** Prion Protein; **NfL:** Neurofilament Light Chain; **CSF:** Cerebrospinal Fluid; **APOE:** Apolipoprotein **E; LRRK2:** Leucine-Rich Repeat Kinase 2; **C9orf72:** Chromosome 9 Open Reading Frame 72; **DaTscan:** Dopamine Transporter Scan; **SPECT:** Single Photon Emission Computed Tomography; **fMRI:** functional Magnetic Resonance Imaging**; DTI:** Diffusion Tensor Imaging; **DW-MRI:** Diffusion-Weighted MRI; **FDG-PET:** Fluorodeoxyglucose-Positron Emission Tomography; **NFT:** Neurofibrillary Tangles; **GBA:** Glucocerebrosidase; **SOD1:** Superoxide Dismutase 1; **mHTT:** mutant HTT; **GRN:** Progranulin; **MBP:** Myelin Basic Protein; **OCBs:** Oligoclonal Bands; **MOG:** Myelin Oligodendrocyte Glycoprotein; **OCT:** Optical Coherence Tomography; **TNF-α:** Tumor Necrosis Factor-Alpha; **IL-6:** Interleukin 6.

ETHICAL STATEMENT

This review paper adheres to ethical research standards. All sources are properly cited to acknowledge the original authors' contributions. No data fabrication, falsification, or plagiarism has been involved in the preparation of this manuscript. The authors have ensured that the work is original and does not infringe on any existing copyrights or intellectual property rights.

SUMMARY

- Biomarkers are essential for early diagnosis of neurodegenerative diseases, which can lead to earlier initiation of treatment and improved outcomes.
- Biomarkers can also be used to track disease progression and predict risk of developing neurodegenerative diseases.
- A variety of biomarkers are available for different neurodegenerative diseases, including amyloid-β, tau, Neurofilament Light chain (NfL) and cerebrospinal fluid biomarkers such as total tau and phosphorylated tau.
- Blood-based biomarkers are emerging as a promising approach for early diagnosis and monitoring of neurodegenerative diseases.
- Advanced neuroimaging techniques, such as Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI), can be used to visualize the underlying structural and functional changes associated with neurodegenerative diseases.
- The integration of biomarkers from different modalities, such as blood, cerebrospinal fluid and neuroimaging, can provide a more comprehensive assessment of disease status.
- Network pharmacology is a promising approach for identifying new drug targets and developing more effective treatments for neurodegenerative diseases.
- Biomarker research is rapidly evolving and there is a need for further development and standardization of biomarkers to improve their clinical utility.

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