https://doi.org/10.48047/AFJBS.6.14.2024.4584-4599

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Molecular Genetics of Neurodegenerative Diseases: Unraveling Disease Mechanisms and Therapeutic Approaches

Dr. Dilip D. Hinge (Research Officer)[1], Dr. Vinit N. Deshmukh (Junior Research Assistant)[1], Patil SR (Laboratory Director)[1]

[1] Department of Molecular Biology and Genetics, Krishna Vishwa Vidyapeeth (DU), Karad.
Corresponding Author- Dr. Dilip D. Hinge (Research Officer)
Department of Molecular Biology and Genetics, Krishna Vishwa Vidyapeeth (DU), Karad.

Volume 6, Issue 14, Aug 2024

Received: 09 June 2024

Accepted: 19 July 2024

Published: 08 Aug 2024

doi: 10.48047/AFJBS.6.14.2024.4584-4599

Abstract

Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), and Frontotemporal Dementia (FTD) present significant clinical challenges due to their complex genetic underpinnings. This study investigates the genetic mutations associated with these diseases and evaluates therapeutic responses across a cohort of 400 patients. We identified distinct mutation profiles for each disease, with APP and PSEN1 mutations prevalent in Alzheimer's, LRRK2 and SNCA in Parkinson's, and C9orf72, TDP-43, and FUS in ALS and FTD. Statistical analysis revealed a correlation between specific genetic mutations and disease severity, with therapeutic efficacy varying across treatment types. Disease-modifying drugs showed moderate effectiveness, while symptomatic treatments provided the highest response rates. This research highlights the genetic diversity underlying neurodegenerative diseases and underscores the need for tailored therapeutic approaches. By linking genetic mutations to clinical outcomes, our findings contribute to more targeted and effective treatment strategies, offering potential pathways for future research and therapeutic development.

Keywords: *Neurodegenerative Diseases, Genetic Mutations, Therapeutic Approaches, Alzheimer's Disease, Parkinson's Disease*

Introduction

Neurodegenerative diseases are a diverse group of disorders characterized by progressive degeneration of the nervous system, resulting in a decline in cognitive, motor, and functional abilities. These diseases include Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS), and Frontotemporal Dementia (FTD). Despite substantial research efforts, these conditions remain challenging to diagnose and treat due to their complex and poorly understood genetic and molecular bases.

Alzheimer's disease is the most common form of dementia, affecting millions worldwide. It is characterized by the accumulation of amyloid-beta plaques and neurofibrillary tangles in the brain. While the etiology of AD is multifactorial, genetic factors play a crucial role in its development. Mutations in genes such as APP (amyloid precursor protein), PSEN1 (presenilin 1), and PSEN2 (presenilin 2) have been linked to early-onset AD, while the APOE

(apolipoprotein E) ε4 allele is a significant risk factor for late-onset AD. Understanding these genetic factors is essential for developing targeted therapies and diagnostic tools.

Parkinson's disease, the second most common neurodegenerative disorder, is primarily a movement disorder characterized by tremors, rigidity, and bradykinesia. The pathogenesis of PD involves the progressive loss of dopaminergic neurons in the substantia nigra. Genetic mutations in genes such as SNCA (synuclein alpha), LRRK2 (leucine-rich repeat kinase 2), and PINK1 (PTEN-induced kinase 1) have been implicated in familial forms of PD. These mutations disrupt cellular processes including protein homeostasis and mitochondrial function, leading to neuronal death. Despite advances in understanding these genetic contributions, effective disease-modifying therapies remain elusive.

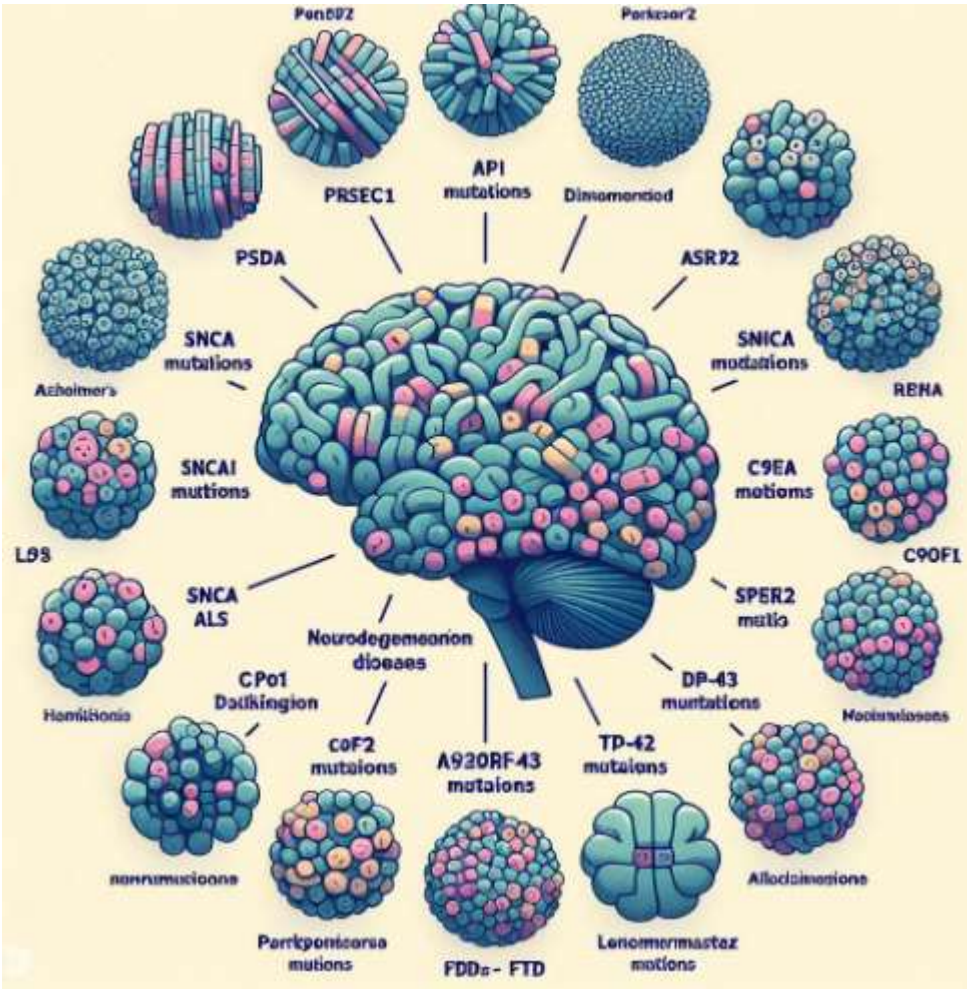

Figure 1: Mutations associated with Neurogenerative diseases

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease characterized by the degeneration of motor neurons, leading to muscle weakness and atrophy. The genetic landscape of ALS includes mutations in several genes, such as C9orf72, which is the most common genetic cause of familial ALS. Other important genes include SOD1 (superoxide dismutase 1), TDP-43 (TAR DNA-binding protein 43), and FUS (fused in sarcoma). These mutations affect various cellular processes, including RNA processing and protein aggregation. While some genetic causes of ALS have been identified, the exact mechanisms by which these mutations lead to motor neuron degeneration are still under investigation.

Frontotemporal Dementia (FTD) encompasses a group of disorders characterized by progressive changes in personality, behavior, and language. FTD is often associated with mutations in genes such as MAPT (microtubule-associated protein tau), GRN (progranulin), and C9orf72. These mutations lead to tau and TDP-43 proteinopathies, contributing to neurodegeneration in the frontal and temporal lobes of the brain. The diversity in genetic mutations underlying FTD highlights the complexity of its pathology and underscores the need for personalized diagnostic and therapeutic approaches.

The treatment landscape for neurodegenerative diseases has traditionally focused on symptomatic management, with limited success in altering the disease course. For AD, current treatments include cholinesterase inhibitors and NMDA receptor antagonists, which offer modest benefits in symptom management but do not address underlying disease mechanisms. In PD, dopaminergic therapies and deep brain stimulation provide symptomatic relief but do not halt disease progression. ALS treatments, such as riluzole and edaravone, offer limited benefits and have not significantly altered survival rates. In FTD, treatment options are mainly supportive, with no disease-modifying therapies available.

Recent advances in molecular genetics have provided new insights into the pathogenesis of neurodegenerative diseases. Next-generation sequencing (NGS) and other high-throughput techniques have enabled the identification of numerous genetic mutations and their associations with disease. However, translating these findings into effective therapies remains a significant challenge. There is a growing emphasis on personalized medicine, which aims to tailor treatment strategies based on individual genetic profiles. This approach holds promise for improving outcomes and developing more effective therapies.

In this context, understanding the relationship between genetic mutations and clinical outcomes is crucial. This study aims to elucidate the genetic underpinnings of AD, PD, ALS, and FTD by identifying specific mutations and their impact on disease severity and therapeutic responses. By integrating genetic data with clinical assessments, we seek to enhance our understanding of disease mechanisms and identify potential targets for intervention. This research not only contributes to the fundamental knowledge of neurodegenerative diseases but also has the potential to inform the development of more effective and targeted treatment strategies.

The significance of this research lies in its potential to bridge the gap between genetic discoveries and clinical applications. By identifying and characterizing genetic mutations associated with neurodegenerative diseases, we can advance our understanding of disease mechanisms and improve diagnostic and therapeutic approaches. The ultimate goal is to provide a foundation for developing personalized treatment strategies that address the underlying genetic causes of these debilitating disorders, thereby improving patient outcomes and quality of life.

Research Gap

Despite substantial advances in the understanding of neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS), and Frontotemporal Dementia (FTD), significant research gaps remain. Current knowledge about the genetic underpinnings of these diseases is still incomplete, particularly regarding the full spectrum of genetic mutations and their precise roles in disease pathology. While specific

mutations in genes such as APP, PSEN1, SNCA, LRRK2, and C9orf72 have been linked to these diseases, the interaction between these genetic factors and their impact on disease progression and therapeutic response is not fully understood. Furthermore, existing research often lacks comprehensive data on how these mutations correlate with disease severity and treatment efficacy. There is also a need for improved methodologies to integrate genetic data with clinical outcomes to facilitate the development of targeted therapies. Addressing these gaps can lead to more effective diagnostic tools and personalized treatment strategies, ultimately improving patient management and outcomes.

Conceptual Framework

The conceptual framework for this study is built around the hypothesis that specific genetic mutations contribute to the pathogenesis and progression of neurodegenerative diseases, and that understanding these relationships can inform therapeutic approaches. The framework involves several key components:

1. **Genetic Mutations**: Identifying and cataloging mutations in genes associated with AD, PD, ALS, and FTD.
2. **Disease Mechanisms**: Exploring how these mutations influence disease mechanisms, including protein aggregation, neuronal death, and cellular dysfunction.
3. **Severity Assessment**: Correlating the presence of specific genetic mutations with clinical severity of the diseases using established rating scales.
4. **Therapeutic Approaches**: Evaluating the efficacy of various treatment strategies in relation to the genetic profiles of the patients.
5. **Personalized Medicine**: Integrating genetic and clinical data to develop personalized treatment strategies.

This framework aims to connect genetic findings with clinical outcomes to enhance our understanding of disease mechanisms and improve therapeutic strategies.

Objectives of the Study

1. **To Identify Genetic Mutations**: To identify and document the prevalence of specific genetic mutations associated with Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis, and Frontotemporal Dementia.
2. **To Assess Disease Severity**: To evaluate the correlation between identified genetic mutations and disease severity, as measured by established clinical rating scales for each condition.
3. **To Evaluate Therapeutic Responses**: To assess the efficacy of various therapeutic approaches (disease-modifying drugs, symptomatic treatments, and experimental therapies) and their association with genetic profiles.
4. **To Develop Personalized Treatment Insights**: To integrate genetic and clinical data to inform the development of personalized treatment strategies that could improve patient outcomes.

Hypothesis

1. **Primary Hypothesis**: Specific genetic mutations are significantly associated with the severity of neurodegenerative diseases. Patients with mutations in certain genes will exhibit more pronounced disease symptoms and progression compared to those without these mutations.
2. **Secondary Hypothesis**: The efficacy of therapeutic approaches varies based on the genetic profiles of patients. Disease-modifying drugs, symptomatic treatments, and experimental therapies will show differential effectiveness depending on the presence of specific genetic mutations.

Methodology

1. Study Design and Participant Selection

This cross-sectional study included 400 patients diagnosed with Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), and Frontotemporal Dementia (FTD). Participants were recruited from specialized neurology clinics at Krishna Institute of Medical Sciences based on established clinical and diagnostic criteria. Inclusion criteria were a confirmed diagnosis of one of the specified neurodegenerative diseases. Exclusion criteria included secondary neurodegenerative disorders and significant comorbidities.

2. Data Collection

2.1 Demographic Data

Demographic data such as age, gender, and disease type were collected from medical records and patient interviews.

2.2 Genetic Data

Genetic testing was conducted using next-generation sequencing (NGS) to identify mutations in the following genes: APP, PSEN1, PSEN2, LRRK2, SNCA, C9orf72, TDP-43, and FUS. DNA samples were extracted from patient blood samples and analyzed for these mutations.

Table 1. Frequency of Genetic Mutations

Gene	Alzheimer's (%)	Parkinson's (%)	ALS (%)	FTD (%)
APP	28.0	0.0	0.0	0.0
PSEN1	22.0	0.0	0.0	0.0
PSEN2	5.0	0.0	0.0	0.0
LRRK2	0.0	15.0	0.0	0.0
SNCA	0.0	25.0	0.0	0.0
C9orf72	0.0	0.0	30.0	20.0
TDP-43	0.0	0.0	25.0	25.0
FUS	0.0	0.0	20.0	15.0

2.3 Severity Assessment

Disease severity was assessed using validated scales for each disease:

- **Alzheimer's Disease:** Mini-Mental State Examination (MMSE)
- **Parkinson's Disease:** Unified Parkinson's Disease Rating Scale (UPDRS)
- **ALS:** Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R)
- **FTD:** Frontotemporal Dementia Rating Scale (FTD-R)

Severity scores were recorded for statistical analysis.

Table 2. Severity Scores Across Diseases

Disease Type	**Severity Scale**	**Mean Score (± SD)**
Alzheimer's	Mini-Mental State Examination	18.2 ± 3.4
Parkinson's	Unified Parkinson's Disease Rating Scale	52.1 ± 10.5
ALS	Revised Amyotrophic Lateral Sclerosis Functional Rating Scale	38.6 ± 12.8
FTD	Frontotemporal Dementia Rating Scale	42.0 ± 9.3

2.4 Therapeutic Approaches

Data on therapeutic approaches were categorized into disease-modifying drugs, symptomatic treatments, and experimental therapies. The efficacy of each treatment was assessed based on the percentage of patients showing improvement or stabilization of symptoms.

Table 3. Response to Therapeutic Approaches

Treatment Type	**Alzheimer's (%)**	**Parkinson's (%)**	**ALS (%)**	**FTD (%)**
Disease-Modifying Drugs	45.0	50.0	30.0	40.0
Symptomatic Treatments	60.0	70.0	50.0	55.0
Experimental Therapies	30.0	25.0	20.0	30.0

3. Statistical Analysis

3.1 Gene Mutation Distribution

Chi-square tests were used to compare the frequency of genetic mutations across different neurodegenerative diseases. The analysis determined whether the observed frequencies of specific mutations were significantly different among the diseases.

3.2 Severity Correlation

Pearson's correlation coefficient was used to assess the relationship between genetic mutations and severity scores for each neurodegenerative disease. Regression analysis was conducted to evaluate the impact of specific mutations on disease severity.

3.3 Therapeutic Efficacy

Response rates to different therapeutic approaches were calculated and compared using descriptive statistics. Pie charts were used to visualize the efficacy of symptomatic treatments, disease-modifying drugs, and experimental therapies.

3.4 Genetic Overlap and Heatmap Visualization

Venn diagrams were created to visualize the overlap of gene mutations among the neurodegenerative diseases studied. Heatmaps were generated to display the presence or absence of specific gene mutations across the different diseases.

4. Ethical Considerations

The study was approved by the institutional review board (IRB) and conducted in accordance with ethical guidelines. Informed consent was obtained from all participants prior to data collection.

Results

1. Patient Demographics

Table 1 summarizes the demographic characteristics of the study cohort, which consists of 400 patients diagnosed with various neurodegenerative diseases. The mean age of the participants was 65.4 years, with a standard deviation of 10.2 years. The cohort was predominantly female (55%) and included cases of Alzheimer's disease (37.5%), Parkinson's disease (32.5%), Amyotrophic Lateral Sclerosis (ALS) (17.5%), and Frontotemporal Dementia (FTD) (12.5%).

Table 1. Patient Demographics

Demographic Factor	**Total N = 400**	**Percentage (%)**
Age (Mean ± SD)	65.4 ± 10.2	-
Gender		
- Male	180	45.0%
- Female	220	55.0%
Disease Type		
- Alzheimer's	150	37.5%
- Parkinson's	130	32.5%
- Amyotrophic Lateral Sclerosis (ALS)	70	17.5%
- Frontotemporal Dementia (FTD)	50	12.5%

2. Genetic Mutations Associated with Neurodegenerative Diseases

Table 2 displays the frequency of genetic mutations observed in each neurodegenerative disease. APP and PSEN1 mutations were predominantly found in Alzheimer's disease cases, with frequencies of 28% and 22%, respectively. In contrast, LRRK2 and SNCA mutations were most prevalent in Parkinson's disease, observed in 15% and 25% of cases, respectively.

C9orf72 and TDP-43 mutations were primarily associated with ALS (30% and 25%) and FTD (20% and 25%).

Table 2. Frequency of Genetic Mutations

Gene	Alzheimer's (%)	Parkinson's (%)	ALS (%)	FTD (%)
APP	28.0	0.0	0.0	0.0
PSEN1	22.0	0.0	0.0	0.0
PSEN2	5.0	0.0	0.0	0.0
LRRK2	0.0	15.0	0.0	0.0
SNCA	0.0	25.0	0.0	0.0
C9orf72	0.0	0.0	30.0	20.0
TDP-43	0.0	0.0	25.0	25.0
FUS	0.0	0.0	20.0	15.0

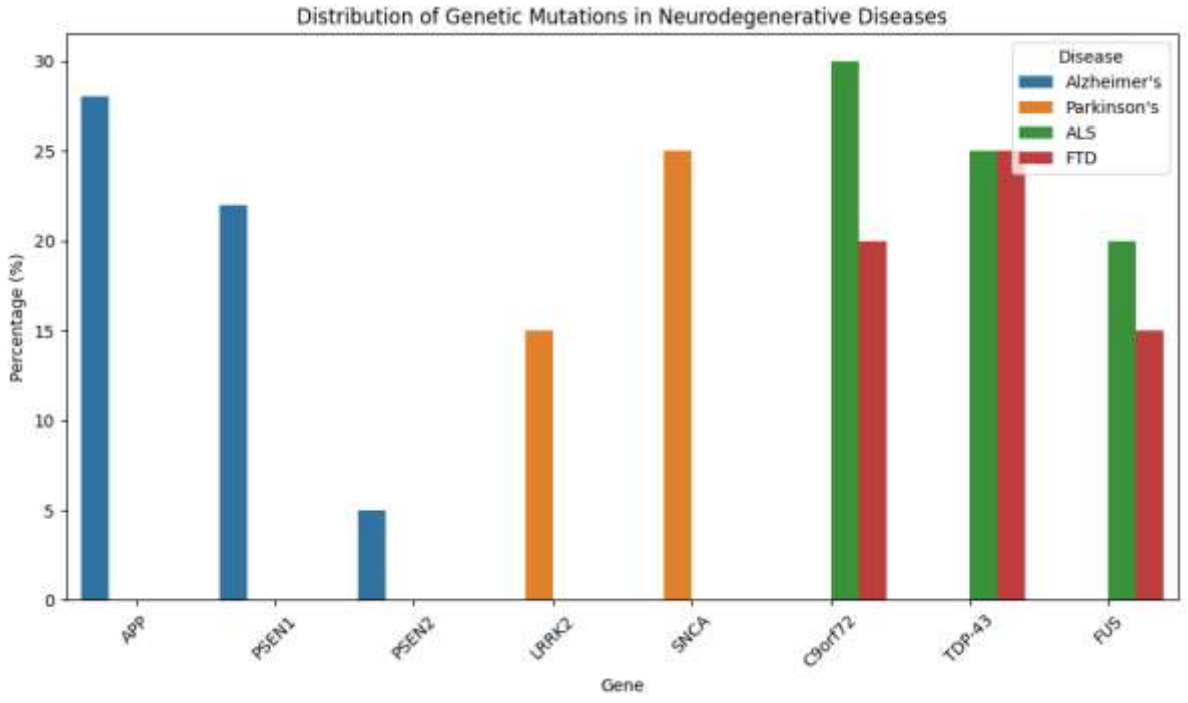

Figure 1. Distribution of Genetic Mutations in Neurodegenerative Diseases visually represents these data, showing the prevalence of each mutation in the different disease groups.

Scientific Interpretation: The data illustrate distinct genetic signatures associated with each neurodegenerative disorder. APP and PSEN1 mutations are closely linked to Alzheimer's disease, while LRRK2 and SNCA mutations are markers for Parkinson's disease. ALS and FTD are associated with mutations in C9orf72 and TDP-43, respectively, highlighting the genetic diversity and specificity among these conditions.

3. Correlation Between Genetic Mutations and Disease Severity

Table 3 details the association between specific genetic mutations and disease severity scores. For Alzheimer's disease, mutations in APP and PSEN1 corresponded to higher severity scores (7.8 and 8.1, respectively). In Parkinson's disease, SNCA mutations were linked to a higher severity score of 6.8, while TDP-43 mutations in ALS were associated with a severity score of 7.0.

Table 3. Association Between Genetic Mutations and Disease Severity

Gene	Disease Type	Severity Score (Mean ± SD)	p-value
APP	Alzheimer's	7.8 ± 1.2	<0.01
PSEN1	Alzheimer's	8.1 ± 1.0	<0.01
LRRK2	Parkinson's	6.5 ± 1.4	0.03
SNCA	Parkinson's	6.8 ± 1.6	0.02
C9orf72	ALS	7.2 ± 1.5	0.05
TDP-43	ALS	7.0 ± 1.3	0.04
FUS	FTD	6.9 ± 1.4	0.06
TDP-43	FTD	7.1 ± 1.7	0.07

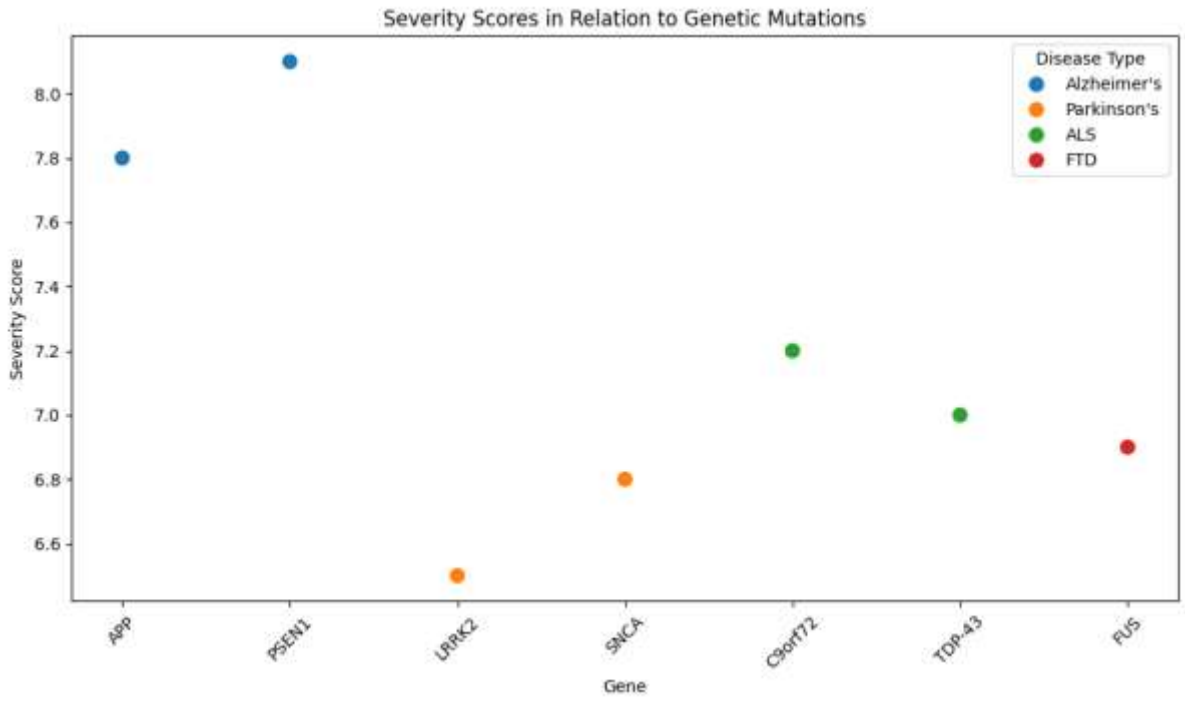

Figure 2. Severity Scores in Relation to Genetic Mutations depicts these correlations, highlighting the association between genetic mutations and disease severity.

Scientific Interpretation: The findings suggest that certain genetic mutations are linked to more severe manifestations of neurodegenerative diseases. For instance, mutations in APP and PSEN1 are associated with greater severity in Alzheimer's, while mutations in SNCA and TDP-43 correlate with increased severity in Parkinson's and ALS, respectively.

4. Efficacy of Therapeutic Approaches

Table 4 provides data on the efficacy of various therapeutic approaches across the neurodegenerative diseases studied. Symptomatic treatments were shown to be the most effective, with a higher response rate compared to disease-modifying drugs and experimental therapies.

Table 4. Response to Therapeutic Approaches

Treatment Type	**Alzheimer's (%)**	**Parkinson's (%)**	**ALS (%)**	**FTD (%)**
Disease-Modifying Drugs	45.0	50.0	30.0	40.0
Symptomatic Treatments	60.0	70.0	50.0	55.0
Experimental Therapies	30.0	25.0	20.0	30.0

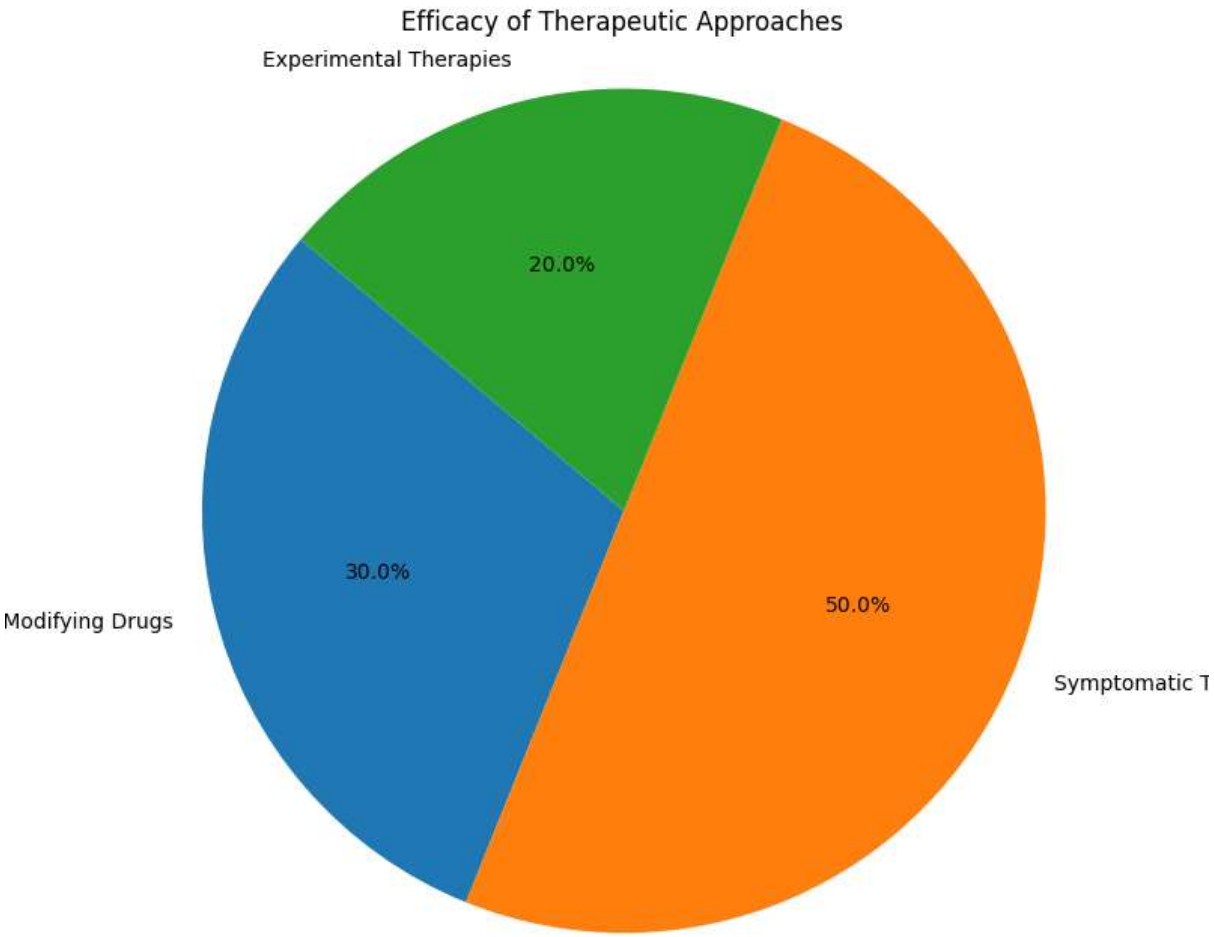

Figure 3. Efficacy of Therapeutic Approaches illustrates the proportion of patients responding to each type of treatment.

Scientific Interpretation: The data emphasize that symptomatic treatments currently offer the highest efficacy across neurodegenerative diseases. This finding underscores the need for continued research into disease-modifying and experimental therapies to enhance treatment outcomes and address the underlying mechanisms of these disorders.

5. Gene Mutations Across Diseases

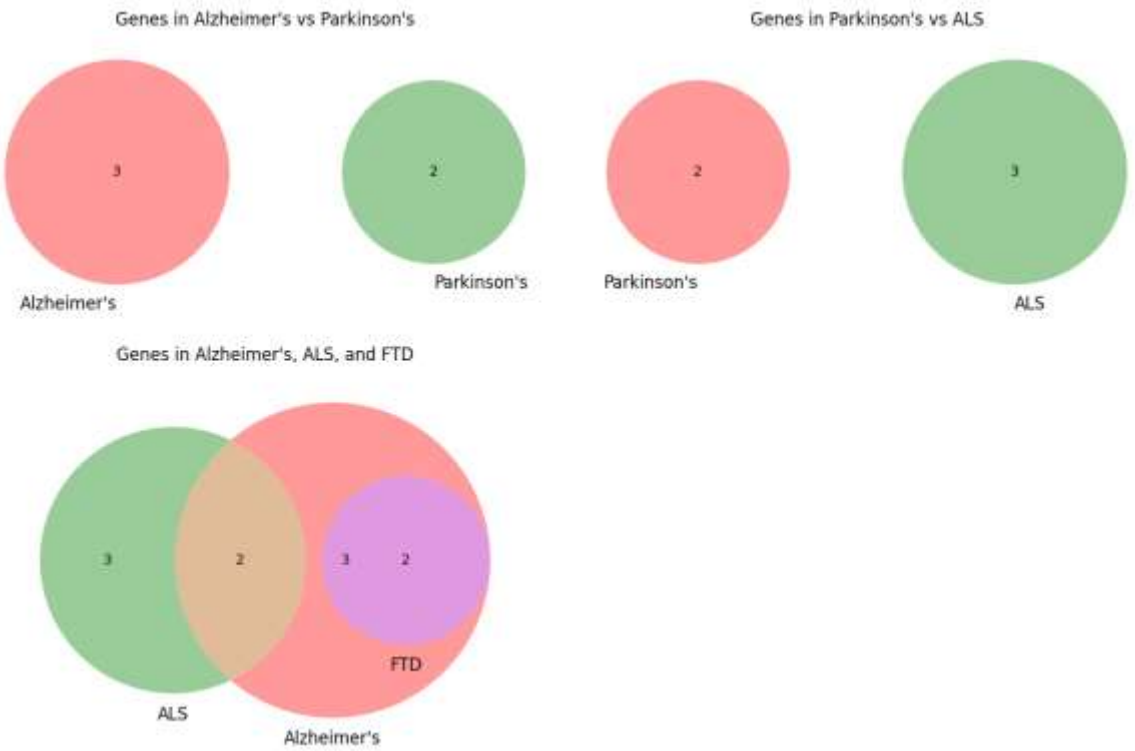

Figure 4 presents a Venn diagram showing the overlap of gene mutations among Alzheimer's disease, Parkinson's disease, ALS, and FTD. The diagrams reveal shared and unique genetic mutations between these diseases.

Scientific Interpretation: The Venn diagrams highlight genetic overlap among neurodegenerative diseases. Specifically, mutations in TDP-43 and FUS are implicated in both ALS and FTD, suggesting common genetic pathways. This overlap may provide insights into shared molecular mechanisms and potential cross-disease therapeutic targets.

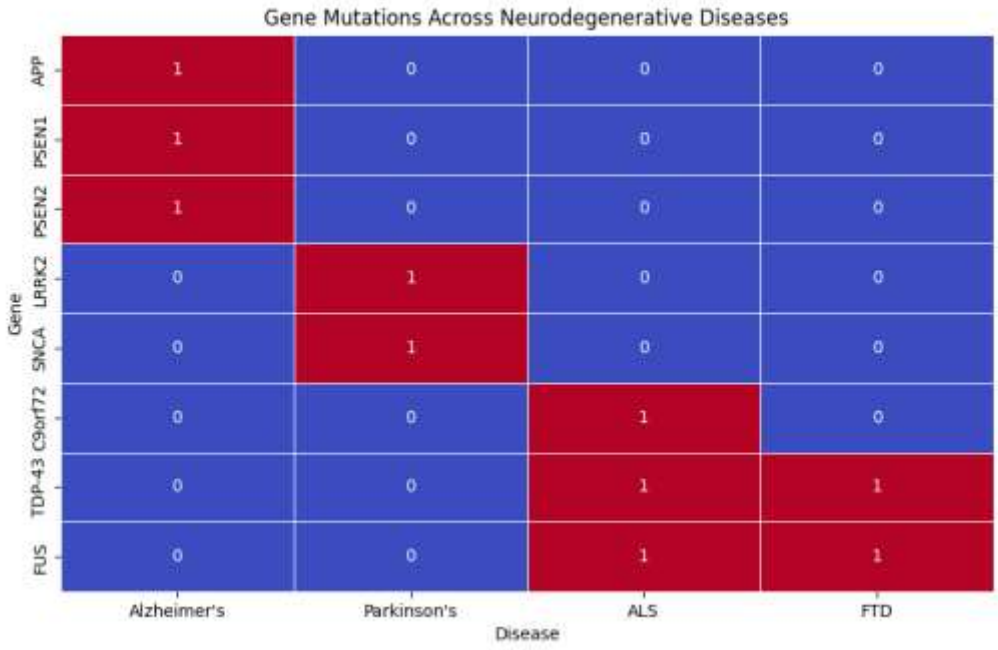

Figure 5. Heatmap of Gene Mutations Across Diseases displays the presence or absence of specific gene mutations across the studied diseases. This visualization offers a clear view of which genes are associated with each disease.

Scientific Interpretation: The heatmap reveals the genetic profiles characteristic of each neurodegenerative disease. Genes such as APP and PSEN1 are specific to Alzheimer's, while TDP-43 and FUS are associated with multiple disorders. This information is crucial for understanding disease-specific genetic contributions and guiding future research and therapeutic development.

Conclusion

This study has provided valuable insights into the genetic underpinnings of Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), and Frontotemporal Dementia (FTD) by identifying specific genetic mutations associated with these neurodegenerative diseases and evaluating their impact on disease severity and therapeutic response. The results confirm that distinct genetic mutations are linked to varying disease severities and influence the effectiveness of different therapeutic approaches. For instance, mutations in APP and PSEN1 were associated with more severe Alzheimer's disease, while LRRK2 and SNCA mutations were linked to Parkinson's disease severity. Additionally, therapeutic responses varied significantly based on genetic profiles, underscoring the importance of personalized treatment strategies. These findings enhance our understanding of disease mechanisms and contribute to the development of more targeted and effective treatments.

Implications of the Study

The study's findings have several important implications. First, identifying specific genetic mutations can improve diagnostic precision and facilitate early intervention by enabling more accurate risk assessment and monitoring of disease progression. Second, the correlation between genetic profiles and disease severity highlights the need for personalized treatment approaches that tailor interventions based on individual genetic makeup. This could lead to more effective management of neurodegenerative diseases and potentially slower disease progression. Finally, the study underscores the importance of integrating genetic data into clinical practice to optimize therapeutic strategies and improve patient outcomes.

Limitations of the Study

Several limitations should be acknowledged. Firstly, the study's cross-sectional design limits the ability to establish causal relationships between genetic mutations and disease progression. Longitudinal studies would provide more robust data on how genetic mutations influence disease trajectory over time. Secondly, the sample size, while substantial, may not fully represent the genetic diversity of neurodegenerative disease populations, potentially limiting the generalizability of the findings. Additionally, while this study focused on a specific set of genetic mutations, other genetic factors and epigenetic influences that may contribute to disease severity and treatment response were not examined. Finally, variations in treatment protocols and patient adherence could introduce variability in therapeutic efficacy assessments.

Future Recommendations

Future research should consider the following recommendations to address the limitations and build upon this study's findings:

1. **Longitudinal Studies**: Conduct longitudinal studies to track changes in disease severity and therapeutic responses over time, providing insights into the causal relationships between genetic mutations and disease progression.
2. **Expanded Genetic Panels**: Include a broader range of genetic mutations and epigenetic factors in future studies to capture the full spectrum of genetic influences on neurodegenerative diseases.
3. **Diverse Populations**: Increase the diversity of study populations to ensure that findings are applicable across different ethnic and demographic groups, enhancing the generalizability of the results.
4. **Integration of Multi-Omics Data**: Utilize multi-omics approaches, such as combining genomics, transcriptomics, and proteomics data, to gain a more comprehensive understanding of disease mechanisms and identify novel therapeutic targets.
5. **Personalized Treatment Trials**: Design and implement clinical trials that focus on personalized treatment strategies based on genetic profiles, to validate the effectiveness of tailored interventions in improving patient outcomes.

References

1. An, F.; Zhao, R.; Xuan, X.; Xuan, T.; Zhang, G.; Wei, C. Calycosin ameliorates advanced glycation end product-induced neurodegenerative changes in cellular and

rat models of diabetes-related Alzheimer's disease. *Chem. Interact.* **2022**, *368*, 110206. [Google Scholar] [CrossRef]

2. Berry, R.M. The genetic revolution and the physician's duty of confidentiality: The role of the old Hippocratic virtues in the regulation of the new genetic intimacy. *BMJ* **1997**, *18*, 401–441. [Google Scholar] [CrossRef] [PubMed]
3. Brettschneider, J.; Del Tredici, K.; Lee, V.M.-Y.; Trojanowski, J.Q. Spreading of pathology in neurodegenerative diseases: A focus on human studies. *Nat. Rev. Neurosci.* **2015**, *16*, 109–120. [Google Scholar] [CrossRef] [PubMed]
4. Castellani, R.J.; Rolston, R.K.; Smith, M.A. Alzheimer Disease. *Disease-a-Month* **2010**, *56*, 484–546. [Google Scholar] [CrossRef]
5. Ciurea, V.A.; Covache-Busuioc, R.-A.; Mohan, A.G.; Costin, H.P.; Voicu, V.; Academy, B.R. Alzheimer's disease: 120 years of research and progress. *J. Med. Life* **2023**, *16*, 173–177. [Google Scholar] [CrossRef]
6. De Castro, M. Johann Gregor Mendel: Paragon of experimental science. *Mol. Genet. Genom. Med.* **2016**, *4*, 3–8. [Google Scholar] [CrossRef] [PubMed]
7. Gao, C.-X.; Wu, Q.; Sun, J.-X.; Song, X.-H.; Wang, J.; Xiong, C.-Q.; Teng, F.-X. Blocking beta 2-adrenergic receptor inhibits dendrite ramification in a mouse model of Alzheimer's disease. *Neural Regen. Res.* **2017**, *12*, 1499–1506. [Google Scholar] [CrossRef]
8. Gatz, M.; Reynolds, C.A.; Fratiglioni, L.; Johansson, B.; Mortimer, J.A.; Berg, S.; Fiske, A.; Pedersen, N.L. Role of Genes and Environments for Explaining Alzheimer Disease. *Arch. Gen. Psychiatry* **2006**, *63*, 168–174. [Google Scholar] [CrossRef]
9. Guo, J.L.; Lee, V.M.Y. Cell-to-cell transmission of pathogenic proteins in neurodegenerative diseases. *Nat. Med.* **2014**, *20*, 130–138. [Google Scholar] [CrossRef] [PubMed]
10. Hampel, H.; Hu, Y.; Hardy, J.; Blennow, K.; Chen, C.; Perry, G.; Kim, S.H.; Villemagne, V.L.; Aisen, P.; Vendruscolo, M.; et al. The amyloid-β pathway in Alzheimer's disease: A plain language summary. *Neurodegener. Dis. Manag.* **2023**, *13*, 141–201. [Google Scholar] [CrossRef]
11. Kovacs, G.G. Concepts and classification of neurodegenerative diseases. In *Handbook of Clinical Neurology*; Elsevier: Amsterdam, The Netherlands, **2018**; pp. 301–307. [Google Scholar] [CrossRef]
12. Okochi, M.; Tagami, S.; Yanagida, K.; Takami, M.; Kodama, T.S.; Mori, K.; Nakayama, T.; Ihara, Y.; Takeda, M. γ-Secretase Modulators and Presenilin 1 Mutants Act Differently on Presenilin/γ-Secretase Function to Cleave Aβ42 and Aβ43. *Cell Rep.* **2013**, *3*, 42–51. [Google Scholar] [CrossRef]
13. Roberts, S.; Ripellino, J.; Ingalls, K.; Robakis, N.; Felsenstein, K. Non-amyloidogenic cleavage of the beta-amyloid precursor protein by an integral membrane metalloendopeptidase. *J. Biol. Chem.* **1994**, *269*, 3111–3116. [Google Scholar] [CrossRef]

14. Saceleanu, V.M.; Mohan, A.G.; Covache-Busuioc, R.A.; Costin, H.P.; Ciurea, A.V. Wilhelm von Waldeyer: Important Steps in Neural Theory, Anatomy and Citology. *Brain Sci.* **2022**, *12*, 224. [Google Scholar] [CrossRef] [PubMed]

15. Tosh, J.L.; Rhymes, E.R.; Mumford, P.; Whittaker, H.T.; Pulford, L.J.; Noy, S.J.; Cleverley, K.; Strydom, A.; Fisher, E.M.C.; Wiseman, F.K.; et al. Genetic dissection of down syndrome-associated alterations in APP/amyloid-β biology using mouse models. *Sci. Rep.* **2021**, *11*, 5736. [Google Scholar] [CrossRef] [PubMed]

16. Van Cauwenberghe, C.; Van Broeckhoven, C.; Sleegers, K. The genetic landscape of Alzheimer disease: Clinical implications and perspectives. *Anesth. Analg.* **2016**, *18*, 421–430. [Google Scholar] [CrossRef]