Journal of Animal & Plant Sciences, 35(6): 2025, Page: 1467-1478
ISSN (print): 1018-7081; ISSN (online): 2309-8694
https://doi.org/10.36899/JAPS.2025.6.0126
Review Article

THE ROLE OF GENE EXPRESSION ALTERATIONS, NON-CODING RNAS, COPY NUMBER VARIATIONS, AND SPLICING IN ALZHEIMER'S DISEASE

S. U. Rehman[1], M. Abdullah[1], K. Soodonbekov[1], B. Kanatov[1] and S. Avtandil[1].

[1]Faculty of Medicine, Ala-Too International University, 720048, Bishkek, Kyrgyzstan.
Corresponding author's Email: shafeeur.rehman@alatoo.edu.kg

ABSTRACT

The neurodegenerative disorder Alzheimer's disease (AD) advances through progressive stages, which cause cognitive deterioration and neuronal death. The study of early-onset AD shows strong connections to APP, PSEN1 and PSEN2 mutations but recent research demonstrates that multiple molecular pathways play essential roles in disease progression. The review integrates existing knowledge about four essential genetic factors that contribute to Alzheimer's disease development: BACE1 and TREM2 expression dysregulation and, non-coding RNAs (e.g., miR-29 and BACE1-AS) and copy number variations (e.g., APP duplications and GRN deletions) and aberrant splicing events (e.g., tau 3R/4R isoform imbalance). The mechanisms work together to disrupt amyloid-beta processing and tau regulation as well as synaptic function and neuroinflammatory pathways which speed up disease progression. The review examines how these factors work together to create AD pathology while discussing their value as diagnostic markers and therapeutic targets. The review demonstrates the need for integrating multiple omics approaches to improve precision medicine approaches for diagnosing and treating Alzheimer's disease. The review demonstrates the intricate nature of AD pathogenesis while advocating for a comprehensive strategy to understand disease mechanisms and create specific therapeutic approaches.

Keywords: Gene Expression, Non-coding RNAs, Copy Number Variations, Splicing

Published first online September 22, 2025 Published final November 30, 2025

INTRODUCTION

AD represents a neurodegenerative disorder which causes dementia leading to progressive memory deterioration before causing death. Since its discovery scientists have linked AD to genetic mutations in APP (Amyloid Precursor Protein) and PSEN1 and PSEN2 genes as they cause early-onset familial AD (Nehra *et al*., 2022; Better, 2023; Hampel *et al*., 2023). AD pathophysiology remains complex because environmental genetic and epigenetic elements play a dynamic part in its development (Nehra *et al*., 2022; Migliore and Coppedè, 2022). A wide range of molecular processes functions as disease initiators and drivers in addition to the established genetic mutations according to recent findings (Dong-Chen *et al*., 2023). The core feature of AD pathology involves gene expression dysregulation which primarily affects essential genes for tau homeostasis neuroinflammation and amyloid-beta production. The BACE1 gene demonstrates elevated expression in AD brains because it produces the β-secretase enzyme which begins APP amyloidogenic processing (Hampel *et al*., 2021). The levels of BACE1 mRNA and protein in AD patients reach approximately 2.5 times those of age-matched controls according to meta-analysis findings (Shobeiri *et al*., 2023).

TREM2 expression patterns undergo changes according to Shi *et al*. (2025) because this gene regulates microglial activation while working to eliminate amyloid plaque. The surface expression of TREM2 in AD brains together with impaired signalling results in weaker immune responses (Shi *et al*., 2025). The tau protein exists in MAPT gene which functions as a crucial element because abnormal MAPT expression leads to tau hyperphosphorylation and neurofibrillary tangles formation (De Bertier *et al*., 2025). Research using RNA sequencing data shows that MAPT overexpression occurs specifically in the entorhinal cortex and hippocampal regions which are affected by AD (Niu *et al*., 2025). AD development depends on the expression control of protein-coding genes and non-coding RNAs (ncRNAs) which function as key regulators of gene expression. Research studies have identified significant changes in miR-29, miR-146a and miR-34c levels in AD brains and CSF which modify tau phosphorylation pathways while affecting neuroinflammation and amyloid-beta production (Sundram *et al*., 2024). The scientific literature shows that miR-29a/b specifically targets BACE1 which leads to higher Aβ production and elevated BACE1 expression (Sharma *et al*., 2024). The formation of BACE1-AS and lncRNAs leads to RNA duplexes that bind to BACE1 mRNA for increased

translation and stability while enhancing Aβ production (Yang *et al*., 2025). These research findings show that ncRNAs offer promise as both therapeutic targets and biomarkers. AD pathophysiology experiences significant effects from copy number variations (CNVs) that describe DNA segment duplications or deletions (Gentile *et al*., 2021). The duplication of APP gene leads to elevated amyloid production and directly causes early-onset AD primarily in familial cases (Grangeon *et al*., 2023). The genes GRN (granulin), CR1 (complement receptor 1), and SORL1 are involved in CNVs that modify immune regulation and lysosomal function and amyloid precursor trafficking (Guo *et al*., 2021). The loss of synaptic genes such as CNTN5 and NRXN1 accelerates cognitive decline because they disrupt synaptic plasticity and connectivity.

Since its discovery Alzheimer's disease has proven difficult to treat despite ongoing research during the past decades (Bermejo and Del, 2024). The medical field still depends on neuropsychological testing alongside neuroimaging for diagnosis but these methods show inadequate sensitivity and specificity during early disease stages (Alzola *et al*., 2024). The medical field offers cholinesterase inhibitors and NMDA receptor antagonists as available treatments that minimize symptoms yet fail to stop neurodegenerative processes (Shukla *et al*., 2025). Leucanemab and donanemab show modest clinical benefits yet raise safety issues after receiving recent FDA approval as anti-amyloid drugs. The limitations in current treatments reveal the urgent need for robust molecular biomarkers along with new therapeutic targets (Ameen *et al*., 2025). The detailed molecular bases of Alzheimer's disease specifically gene expression dysregulation non-coding RNA networks CNVs and aberrant splicing offer promising paths for both therapeutic development and diagnostic precision. Figure 1 illustrates the biological mechanisms that contribute to Alzheimer's disease development.

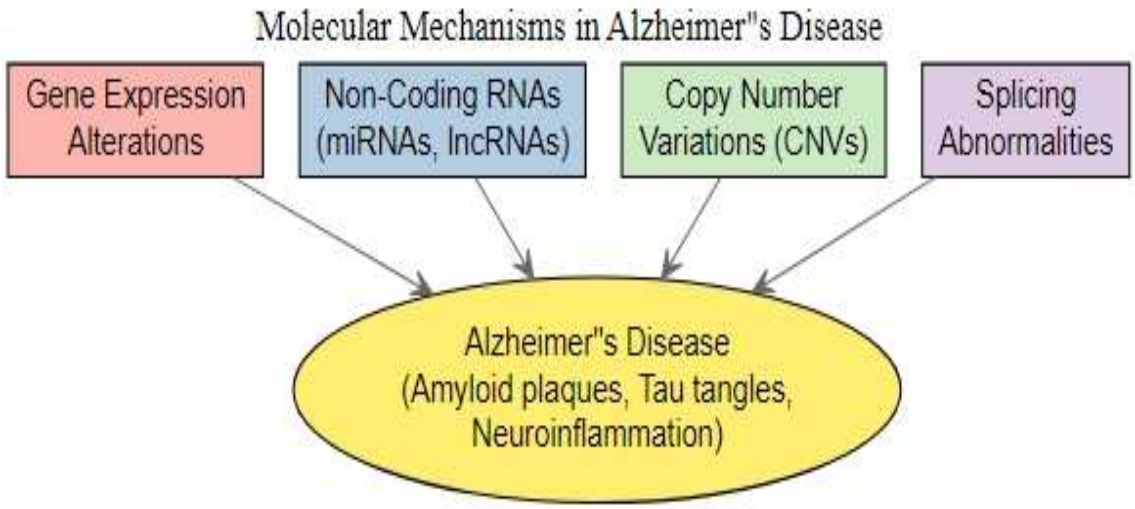

Figure 1. The figure demonstrates how Alzheimer's disease progresses at a molecular level. The disease pathology results from four main factors including Gene Expression Alterations (red box). The changes in gene regulation might impact neurodegenerative processes. Non-Coding RNAs (miRNAs, lncRNAs) (blue box) the regulatory effects of small and long non-coding RNAs on gene expression contribute to disease progression. Copy Number Variations (CNVs) (green box) Structural genomic variations which modify gene dosage and neuronal function. The function of normal proteins becomes disrupted due to Splicing Abnormalities (purple box). The process of RNA splicing creates errors which can disrupt proper protein function.

Gene Expression Alterations in Alzheimer's disease: The main characteristic of Alzheimer's disease is widespread gene expression dysregulation that results in neuronal dysfunction and neurodegeneration. The complex process of transcription factor imbalances combined with epigenetic changes and ongoing neuroinflammatory responses generates this altered transcriptional landscape (Giallongo *et al*., 2022). Epigenetic mechanisms which include histone tail modifications and DNA methylation at CpG islands and chromatin remodelling enable the regulation of important genes related to immune response and synaptic and amyloid processing function (Maity *et al*., 2021). The promoter regions of neuroprotective genes SORL1 and NEP show aberrant hypermethylation but pro-amyloidogenic genes BACE1 display hypomethylation leading to their increased expression in AD brain tissue (Tiwari *et al*., 2025). The AD brain shows distinct histone acetylation patterns through H3K9ac and H3K27ac

markers near immune and amyloid metabolism enhancers (Paniri *et al*., 2024).

BACE1 β-secretase enzyme displays increased expression in AD brains through epigenetic promoter relaxation which leads to more amyloid-beta production. BACE1 mRNA expression in the hippocampus of Alzheimer's patients reaches 2.5 times higher levels than in controls with similar ages according to RNA-seq data (Zhou *et al*., 2023). NF-κB and SP1 bind more frequently to the BACE1 promoter under oxidative and inflammatory stress conditions while decreased promoter methylation contributes to these binding events (Luo *et al*., 2024). The regulation of TREM2 microglial receptor which handles phagocytosis and plaque removal functions becomes dysregulated. TREM2 loses its functional communication abilities through mutations like R47H but its reduced expression occurs through histone repression modifications and DNA methylation in regulatory areas (Shi *et al*., 2025). The research of ChIP-seq data reveals that the TREM2 promoter in AD brains contains increased levels of the repressive histone mark H3K27me3 which leads to decreased transcription in microglial subtypes (Scholz *et al*., 2024).

SNCA (alpha-synuclein) joins BACE1, TREM2, and MAPT among the important genes that exhibit dysregulation in recent transcriptomic studies about Alzheimer's disease. Research now shows that SNCA links primarily to Parkinson's disease yet new findings suggest its role in Alzheimer's disease pathogenesis. The synaptic protein alpha-synuclein serves the biological functions of synaptic plasticity and neurotransmitter release and synaptic vesicle movement because it is encoded by the SNCA gene. The decreased expression of SNCA in Alzheimer's disease brains particularly affects the cortex and hippocampus thus causing synaptic dysfunction and cognitive deficits (Murphy and McKernan, 2022; Thangavelu *et al*., 2024). Multiple AD cohorts have demonstrated through RNA-seq data a significant reduction in SNCA mRNA levels with a $\log_2$FC −1.4 and $p < 0.01$ (Rey *et al*., 2021). The decreased resistance to oxidative stress together with compromised synaptic signaling appear to be responsible for the observed downregulation. Alpha-synuclein forms connections with tau and amyloid-beta which could increase protein aggregation while triggering neuroinflammatory responses. In AD the reduction of SNCA expression helps cause synaptic breakdown together with increased neurodegenerative pathways.

The tau protein gene MAPT is controlled by alternative splicing mechanisms. The splicing factors SRSF1 and TRA2B exhibit improper regulation in AD patients which leads to unbalanced 3R/4R tau isoform expression (Corsi *et al*., 2022). DNA hypomethylation coupled with histone acetylation modifications at MAPT intronic enhancers leads to increased tau expression alongside exon 10 inclusion which results in the formation of neurofibrillary tangles. The combination of epigenetic changes and transcription factor malfunction together with persistent inflammation from reactive astrocytes and activated microglia leads to enduring changes in gene expression profiles that negatively affect metabolic equilibrium and synaptic communication and neuroprotective systems. The expression patterns of hundreds of genes from immune pathways (e.g. TREM2, CD33), metabolic pathways (BACE1, SORL1) and cytoskeletal pathways (MAPT, NEFL) remain altered according to RNA-seq profiling of AD-affected brain regions (Zhang *et al*., 2023). Gene expression changes together with their regulatory mechanisms that occur in Alzheimer's disease are summarized in Figure 2 and Table 1.

Table 1. The gene involved in Alzheimer's disease (AD). Alteration: The upregulation or downregulation of the gene expression in AD. Impact: The biological effects or role of the gene alteration in the pathogenesis of AD. Pathway: The affected biological pathways involved in AD progression (e.g., amyloid-beta pathway, tau pathology, immune response).

Gene	Alteration	Impact	Specific Pathway	References
BACE1	Upregulated	Increased amyloid-beta (Aβ) production	APP cleavage → β-secretase pathway (BACE1–APP–γ-secretase axis)	(Wang *et al*., 2024)
TREM2	Upregulated	Impaired microglial activity and immune signaling	TREM2–DAP12–SYK signaling cascade	(Zhou *et al*., 2023)
MAPT	Upregulated	Tau hyperphosphorylation and aggregation	GSK3β/PP2A-regulated tau phosphorylation pathway	(Pan *et al*., 2021)
APOE (ε4 allele)	Upregulated	Impaired Aβ clearance, disrupted lipid transport	APOE4–LDLR/LRP1–Aβ clearance axis; lipid metabolism dysregulation	(D'Alonzo *et al*., 2023)
GRN	Downregulated	Altered lysosomal function, enhanced neuroinflammation	Progranulin–Sortilin–lysosomal axis; NF-κB-mediated inflammatory pathway	(Wang *et al*., 2022)
SNCA	Downregulated	Synaptic dysfunction and α-synucleinopathy	SNCA–Rab3a–SNARE vesicle transport pathway; α-synuclein degradation via autophagy	(Rey *et al*., 2021)

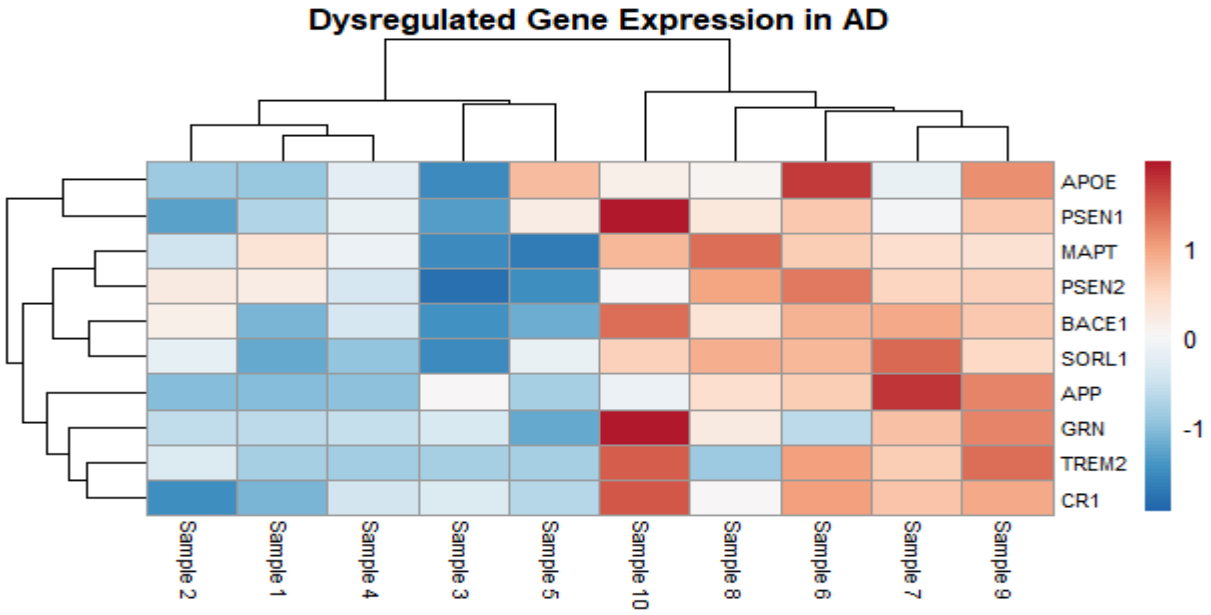

Figure 2. The heatmap based on post-mortem brain tissue samples of AD patients and age-matched healthy controls displays the gene expression dysregulation patterns of AD. The color scale in the heatmap displays normalized expression levels with blue indicating downregulation and white showing neutral baseline expression and red indicating upregulation. The heatmap contains brain sample columns that represent individual brain tissue samples and gene rows that represent APOE, PSEN1, MAPT, APP, BACE1, SNCA and other genes. The average linkage method with Pearson correlation distance metric performs hierarchical clustering to group genes and samples. The clustering method groups genes and samples with similar expression patterns to show individual differences in gene regulation and identify distinct molecular AD signatures.

The APOE gene along with its APOE4 allele plays a significant role in developing AD. Research has established that the APOE4 allele increases AD risk because it disrupts lipid metabolism and amyloid-beta clearance processes (Ayyubova, 2024). The APOE4 allele carriers demonstrate reduced amyloid-beta processing capabilities which leads to brain accumulation of this protein. The numerous pathways which are altered in AD have been identified through gene expression profiling studies including those that affect neuronal survival and synaptic plasticity and immune regulation (Koutsodendris *et al*., 2022). Research has demonstrated that AD pathology leads to widespread transcriptional dysregulation while the disease mechanisms remain complex.

Non-Coding RNAs and Their Roles in AD: Non-coding RNAs (ncRNAs) contain two significant post-transcriptional regulators of gene expression including microRNAs and long non-coding RNAs (lncRNAs) which affect numerous biological processes according to Statello *et al*. (2021). Research shows that Alzheimer's disease (AD) exhibits dysfunctional noncoding RNAs (ncRNAs) which control crucial pathological mechanisms involving tau phosphorylation along with amyloid-beta (Aβ) formation and synaptic damage and neuroinflammatory responses (Olufunmilayo and Holsinger, 2023). The primary outcome of miRNA binding to target mRNA 3′ untranslated regions (3′UTRs) occurs through translational repression and mRNA degradation processes. Studies have found that several miRNAs change their expression levels in AD patients while showing associations with disease-related pathological features. AD patients show downregulation of miR-29a/b by 2.3 times which leads to increased BACE1 enzyme activity because this enzyme processes APP into amyloidogenic forms (Nguyen *et al*., 2021); The negative regulator miR-146a shows elevated expression levels between 1.7 to 2.5 times which becomes abnormal during chronic AD-related neuroinflammation (Li *et al*., 2023).

The AD-related elevation of miR-34c drives tau phosphorylation through its ability to target protein phosphatases and kinases thus producing neurofibrillary tangles. Blood tests of miR-29 and miR-146a show promise as diagnostic tools because research data shows that miR-29a achieves an area under the ROC curve (AUC) of 0.82 while maintaining 78% sensitivity and 80% specificity for detecting AD patients versus healthy controls. The miR-132 miRNA shows significant reduction of 3–4 times in both AD brains and cerebrospinal fluid (CSF) samples. Through its protective

mechanisms miR-132 maintains synaptic health as well as survival and plasticity of neurons. The miR-132 targets two crucial mRNAs including MeCP2 which functions as a transcriptional repressor for neuronal maturation and epigenetic control and p250GAP that acts as a dendritic spine developmental inhibitor (Chen *et al*., 2021; Ilieva, 2024). The decreased levels of miR-132 in AD patients create conditions that lead to increased neuronal damage together with dendritic shrinkage and impaired synaptic transmission. The pathophysiology of AD experiences major regulatory influence through the action of long non-coding RNAs (lncRNAs) in addition to miRNAs. BACE1-AS acts as an antisense lncRNA that forms RNA-RNA duplexes to stabilize BACE1 mRNA and increase β-secretase activity and Aβ production (Bampatsias *et al*., 2022). According to Olufunmilayo and Holsinger (2023), 17A functions as a lncRNA that leads to incorrect tau exon 10 splicing resulting in toxic tau forms which help create neurofibrillary tangles. NEAT1 together with MALAT1 represent two AD-dysregulated lncRNAs that control inflammation and regulate nuclear paraspeckle function.

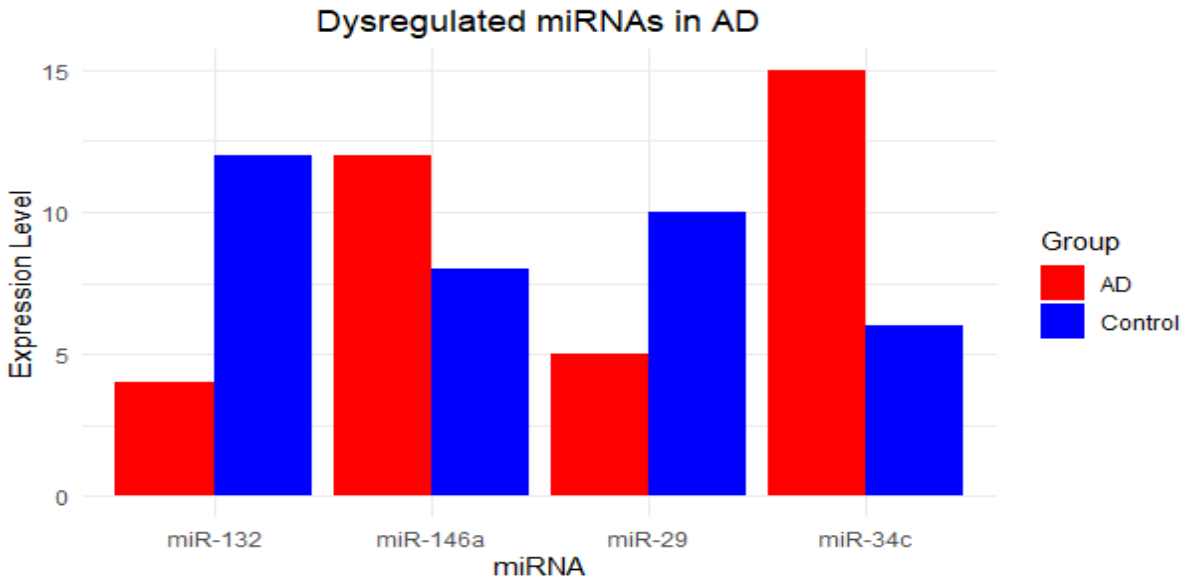

Figure 3. The expression of important microRNAs (miRNAs) differs in Alzheimer's disease (AD). Post-mortem brain tissue samples from AD patients (red) and age-matched controls (blue) display the expression levels of four disease-associated miRNAs: miR-132, miR-146a, miR-29 and miR-34c. Multiple transcriptomic investigations were used to generate the data which is presented as averaged normalised counts. The expression of miR-146a and miR-34c increases in AD brains due to their roles in tau phosphorylation, amyloid-beta processing, neuroinflammation and synaptic integrity while miR-132 and miR-29 experience significant decreases. The DESeq2 analysis used hierarchical clustering and differential expression methods with $p < 0.05$ as the significance threshold.

The majority of research demonstrates consistent directional dysregulation of these miRNAs in AD brain tissue even though cohort-dependent variability is observed in biofluid samples such as CSF and plasma. The levels of miR-146a increase in AD brain tissues but its expression in plasma and serum shows conflicting results. Such findings could result from either sample processing steps or stage-specific changes or degradation processes (Azam *et al*., 2024). The brain tissue shows consistent downregulation of miR-132 but some research studies fail to validate this pattern in blood-based biomarker panels. This underlines the necessity to perform cross-validation between multi-omics platforms as well as across different sample types when interpreting miRNA biomarker data while also considering the importance of tissue context.

Copy Number Variations in AD Pathogenesis: Copy number variations (CNVs), the duplication or deletion of specific genomic regions, are now important causes of neurodegenerative disorders including Alzheimer's disease (AD) (Gentile *et al*., 2021). The CNVs may cause gene expression changes which may influence the key cellular functions like amyloid-beta synthesis, immune responses and synaptic transmission (Wang *et al*., 2023). These genetic changes in AD contribute to the complex genetic basis of the disease which leads to the genetic heterogeneity observed in affected individuals (Andrews *et al*., 2023). Personal genomic evaluations for AD risk prediction should include CNVs as an essential component. The most common reason for early onset AD is a high copy number variation of the APP gene (Ming *et al*., 2022; Ehn *et al*., 2025). This duplication results in the

elevated levels of amyloid precursor protein (APP), thus resulting in the enhanced production of amyloid-β peptides that form plaques in the brain, a characteristic feature of AD (Zargaham *et al*., 2025). The immune system and amyloid processing are affected by CNVs in genes GRN (granulin), CR1 (complement receptor 1) and SORL1 (sortilin-related receptor 1) (Firdaus and Li, 2024). These genes play a role in regulating microglial functions and amyloid turnover but their downregulation due to CNVs leads to neuroinflammation and dysregulation of amyloid beta processing which worsens the AD progression (Yang *et al*., 2025). Also, deletions in genes such as CNTN5 (contactin 5) and NRXN1 (neurexin 1) have been linked to AD (Dauar *et al*., 2023).

Copy number variations (CNVs) play a significant role in Alzheimer's disease (AD) particularly in early cases. WGS, aCGH and SNP arrays are commonly used to identify CNVs as high-resolution platforms with different sensitivity levels and breakpoint resolution. High-resolution platforms that offer varying degrees of sensitivity and breakpoint resolution, such as whole-genome sequencing (WGS), array comparative genomic hybridisation (aCGH), and single nucleotide polymorphism (SNP) arrays, are commonly used to identify CNVs. The duplication of the APP gene, which raises the levels of amyloid precursor protein and causes an excess of amyloid-beta peptides, is one of the best-characterized CNVs. This duplication causes 8–10% of autosomal dominant early-onset AD and has nearly complete penetrance and a significant effect size. People who have APP duplication frequently exhibit earlier disease onset and co-occurring cerebral amyloid angiopathy (Hoogmartens *et al*., 2021; Leitner *et al*., 2024). Duplications and deletions affecting genes like GRN, CR1, and SORL1 are examples of additional harmful CNVs. For example, deletions in exons 2–5 of GRN impair lysosomal function and increase neuroinflammation by disrupting progranulin production. For instance, duplications spanning intron 5 to exon 8 of CR1 change complement regulation and raise plaque-associated inflammation, while CNVs disrupting exon 13–20 of SORL1 impair its function in APP trafficking.

The genes control synaptic connection preservation and neuron health which leads to synaptic dysfunction when deleted. The first sign of Alzheimer's disease synaptic dysfunction occurs due to CNVs in these genes which produces early cognitive decline in patients. The presence of genetic heterogeneity in Alzheimer's disease caused by CNVs requires personalized genomic analyses to enhance risk prediction and early detection and potentially develop better treatments for AD patients with genetic risk. Scientists continue to study this interaction while understanding how CNVs and environmental risk factors like head trauma and cardiovascular stress affect disease expression and progression. Research into AD diagnostic precision and gene-dosage-based treatment methods depends on the understanding of CNV architecture together with its interactions with other modifying factors. The figure shows copy Number Variations in AD Pathogenesis.

Alternative Splicing and Its Impact on AD: The process of alternative splicing functions as a fundamental neuronal system which produces various proteins from single genes that execute distinct cellular functions. The disease progression of Alzheimer's disease (AD) develops from splicing abnormalities which create abnormal protein variants (Biamonti *et al*., 2021; Bhatnagar *et al*., 2023). The disrupted splicing regulation affects many critical genes that preserve neuronal architecture and regulate amyloid-beta breakdown as well as synaptic operations (Lui *et al*., 2025). Research on neurodegeneration shows that irregular splicing patterns act as a critical factor for disease development which makes splicing regulation an appealing therapeutic approach for treating Alzheimer's disease (Nikom *et al*., 2023). AD splicing dysfunction primarily affects the tau protein because its alternative splicing creates two main isoforms that have either three (3R) or four (4R) microtubule-binding repeat domains (Waheed *et al*., 2023). The AD progression results in a disturbance of 3R/4R tau isoform ratios that leads to elevated 4R tau levels. The faulty tau splicing process leads to the formation of neurofibrillary tangles through tau aggregation which are the main pathological feature of AD (Waheed *et al*., 2023). The tangles cause significant damage to neurons that leads to cell death specifically in brain areas that control memory and cognitive functions. Tau splicing regulation plays an essential role in determining the course of Alzheimer's disease progression (Sinsky *et al*., 2021). The amyloid precursor protein (APP) gene exhibits critical involvement in AD through its alternative splicing pathways which regulate its processing activity and amyloid-beta peptide generation (López-Hernández *et al*., 2025). During the processing stage different APP splicing variants determine how amyloid-beta peptides will be formed. The accumulation of these peptides leads to amyloid plaque formation which serves as a main feature of AD pathology. The SNCA gene which encodes alpha-synuclein and the BIN1 gene which regulates synaptic function and neuroinflammatory processes display splicing defects in AD brains (Ramakrishan *et al*., 2025). The breakdown of synaptic communication along with intensified neuroinflammatory responses through splicing alterations speeds up neurodegenerative processes. The therapeutic application of targeting splicing mechanisms offers potential solutions to treat AD-related abnormalities and extend disease progression thus opening new therapeutic possibilities for AD treatment. Figure 5 illustrates the MAPT gene's alternate splicing pattern of exon 10 that produces an increased abundance

of tau protein variants in AD. The pie chart shows the distribution of 3-repeat tau (3R tau) and 4-repeat tau (4R tau) isoforms in AD post-mortem brain tissue samples. The RNA-seq and RT-PCR quantification from AD brain samples demonstrates that 4R tau forms approximately 70% of total tau transcripts but 3R tau represents only 30%. The evidence points to an abnormal process of exon 10 inclusion. The neurofibrillary tangles which form as a result of this imbalance lead to microtubule instability and promote tau aggregation. The studies consistently show this 3R/4R tau ratio pattern although some variations in brain region-specific and disease progression-related ratios have been documented (Corsi *et al*., 2022; Yin *et al*., 2024)

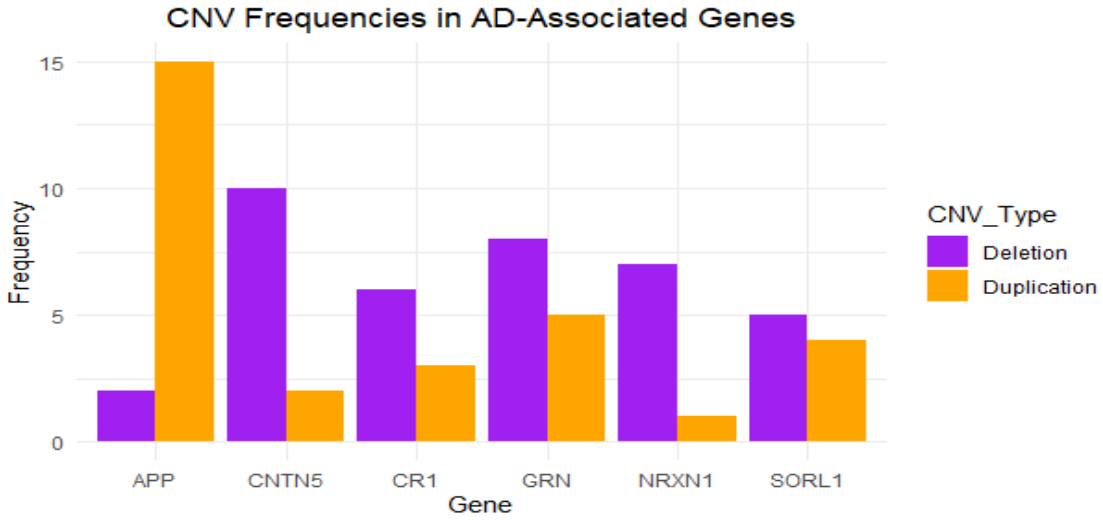

Figure 4. **The figure illustrates the copy number variation (CNV) frequencies specifically deletions and duplications in several Alzheimer's disease (AD)-associated genes. The APP gene shows the highest frequency of duplications (n=15), suggesting its strong association with increased amyloid-beta production in AD pathology. In contrast, CNTN5, GRN, and NRXN1 exhibit higher frequencies of deletions compared to duplications, indicating potential loss-of-function effects contributing to synaptic and neuroinflammatory dysfunction. CR1, SORL1, and GRN demonstrate relatively balanced CNV types, while NRXN1 shows a striking imbalance favoring deletions. Overall, the plot highlights gene-specific patterns of CNVs that may underlie different pathogenic mechanisms in AD.**

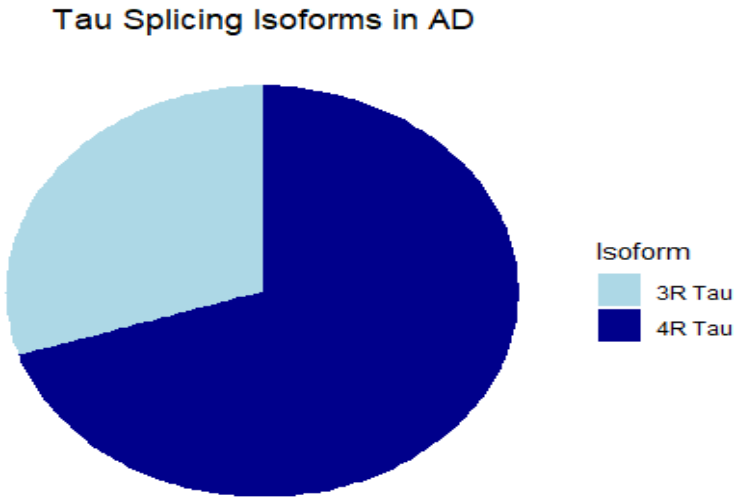

Figure 5. The figure presents the relative distribution of tau splicing isoforms 3R Tau and 4R Tau in Alzheimer's disease (AD). The pie chart shows that 4R Tau isoforms (dark blue) are more predominant, accounting for approximately two-thirds of the total tau population, while 3R Tau isoforms (light blue) comprise the remaining one-third. This imbalance between 3-repeat (3R) and 4-repeat (4R) tau isoforms is a hallmark of tauopathies and contributes to microtubule instability, tau aggregation, and the formation of neurofibrillary tangles in AD pathology.

The imbalance between 3-repeat (3R) and 4-repeat (4R) tau isoforms in Alzheimer's disease (AD) results from strict control of exon 10 alternative splicing in the MAPT gene by SRSF1, TRA2B, and hnRNPG splicing factors. The elevated production of SRSF1 in AD triggers the inclusion of exon 10 and results in elevated 4R tau levels that show higher propensity to form neurofibrillary tangles. The unbalanced production of 3R and 4R tau causes fast neuronal degeneration while destabilizing microtubules. Scientists use RNA-seq data and sophisticated tools like rMATS, MAJIQ and SUPPA2 to measure exon inclusion levels and detect differential splicing events between conditions. These tau splicing changes occur specifically in the entorhinal cortex and hippocampus regions and their presence increases with disease progression according to Braak stages (Li *et al*., 2023. The alternative splicing of APP generates different isoforms containing Kunitz protease inhibitor (KPI) domains including APP751 and APP770 which exhibit increased expression in AD brains to promote amyloidogenic processing. The alternative splicing of SNCA produces truncated isoforms including SNCA112 that lack the central hydrophobic domain which affects their aggregation properties and induces synaptic dysfunction. The splicing alterations serve as both diagnostic markers and therapeutic targets which correspond to disease stage and brain region thus demonstrating the essential role of post-transcriptional regulation in AD.

Conclusion and Future Perspectives: Multiple molecular disruptions including aberrant splicing events and copy number variations (CNVs) and dysregulation of non-coding RNA (ncRNA) and gene expression alterations combine to produce Alzheimer's disease (AD) and its disease progression. The individual components act as barriers that impede essential cellular operations including tau aggregation and amyloid-beta accumulation and synaptic dysfunction and long-term neuroinflammation. These pathways undergo additional post-transcriptional modifications through ncRNAs including miRNAs and lncRNAs and transcriptional dysregulation affects the expression of vital genes BACE1 and MAPT. Neurodegeneration worsens because CNVs which affect immune-related genes CR1, GRN and endosomal trafficking genes SORL1 while splicing errors disrupt APP processing and tau isoform ratios. The complete understanding of these intricate relationships requires future studies to use multi-omics approaches which combine genomic, transcriptomic, proteomic and epigenomic data.

The integration of these methods becomes possible for biomarker and treatment target discovery through the use of complex analytical methods such as co-expression network analysis and Bayesian network modelling and supervised machine learning. The Religious Orders Study and Memory and Ageing Project (ROSMAP) and the Accelerating Medicines Partnership Alzheimer's Disease (AMP-AD) collaborative initiatives have developed extensive public multi-omics datasets that originate from thoroughly described post-mortem brain tissues. These resources function as essential integrative research platforms because they generate high-resolution molecular maps which span disease progression and brain regions. Through precise computational models' scientists can identify particular molecular signatures including CNVs and splicing isoforms and ncRNA expression profiles that will direct personalized treatment strategies. The future development of AD therapies depends on our ability to decode individual molecular profiles of patients and create personalized therapeutic approaches.

Acknowledgments: The authors are thankful to Ala-Too International University for financial support and rewards for publication.

Conflicts: The authors have no conflict of interest

Funding Sources: No grant was available for this study.

Consent Statement: The authors declare that no human or animal subjects were involved in the preparation of this manuscript. All data included in the review were obtained from publicly available sources, and proper citations are provided for all referenced work. The authors have no conflicts of interest to declare and are committed to upholding the ethical guidelines for scientific publishing.

Author Contributions: Shafee Ur Rehman collected the data and wrote the manuscript. Muhammad Abdullah, Kylym Soodonbekov, Baiaman Kanatov, and Saiddin Avtandil reviewed and edited the final manuscript file.

REFERENCES

Ameen, T. B., U. Ali, S. Omer, A.S. Muhammad, I.A.S. Muhammad, N.K. Samina, A.A. Muhammad, A. Muhammad, K. Muhammad, S.A.S. Muhammad and A. Raheem (2025). Amyloid solutions: lecanemab, gantenerumab, and donanemab in the treatment of Alzheimer's disease. Egypt. J. Neurol. Psychiatry Neurosurg. 61(1): 1-26. https://doi.org/10.1186/s41983-025-00968-3

Alzola, P., C. Carnero, F. Bermejo-Pareja, G. Sanchez-Benavides, J. Pena-Casanova, V. Puertas-Martin, B. Fernandez-Calvo and I. Contador (2024). Neuropsychological assessment for early detection and diagnosis of dementia: current knowledge and new insights. J. Clin. Med. 13(12): 3442. https://doi.org/10.3390/jcm13123442

Andrews, S.J., A.E. Renton, B. Fulton-Howard, A. Podlesny-Drabiniok, E. Marcora and A.M. Goate (2023). The complex genetic architecture of Alzheimer's disease: novel insights and future directions. EBioMedicine. 90: 104511. https://doi.org/10.1016/j.ebiom.2023.104511

Ayyubova, G. (2024). Apoe4 is a risk factor and potential therapeutic target for Alzheimer's disease. CNS Neurol. Disord. Drug Targets. 23(3): 342-352. https://doi.org/10.2174/1871527322666230303114425

Azam, H.M., R.R. Isabel, G. Christian, K.M. Muhammad, D. Florian, H. Katja, P. Harald, H. Barbara, R. Dirk, S. Peter and R. Stefan (2024). MicroRNA biomarkers as next-generation diagnostic tools for neurodegenerative diseases: a comprehensive review. Front. Mol. Neurosci. 17: 1386735. https://doi.org/10.3389/fnmol.2024.1386735

Bampatsias, D., I. Mavroeidis, S. Tual-Chalot, N.I. Vlachogiannis, F. Bonini, M. Sachse, G. Mavraganis, A. Mareti, C. Kritsioti, A. Laina and D. Delialis (2022). Beta-secretase-1 antisense RNA is associated with vascular ageing and atherosclerotic cardiovascular disease. Thromb. Haemost. 122(11): 1932-1942. https://doi.org/10.1055/a-1914-2094

Better, M.A. (2023). Alzheimer's disease facts and figures. Alzheimers Dement. 19(4): 1598-1695. https://wehco.media.clients.ellingtoncms.com/news/documents/2024/03/19/Alzheimers_report.pdf

Bermejo, P.F and T.S. Del (2024). Controversial past, splendid present, unpredictable future: a brief review of Alzheimer disease history. J. Clin. Med. *13*(2): 536. https://doi.org/10.3390/jcm13020536

Bhatnagar, A., K. Krick, B.C. Karisetty, E.M. Armour, E.A. Heller and F. Elefant (2023). Tip60's novel RNA-binding function modulates alternative splicing of pre-mRNA targets implicated in Alzheimer's Disease. J. Neurosci. 43(13): 2398-2423. https://doi.org/10.1523/ JNEUROSCI.2331-22.2023

Biamonti, G., A. Amato, E. Belloni, A. Di Matteo, L. Infantino, D. Pradella and C. Ghigna (2021). Alternative splicing in Alzheimer's disease. Aging Clin. Exp. Res. 33: 747-758. https://doi.org/10.1007/s40520-019-01360-x

Chen, D. and S. Lee (2021). The dynamic regulatory role of miR-132 in adult hippocampal neurogenesis and neural stem cell development. Undergrad. Res. Nat. Clin. Sci. Technol. J. 5: 1-7. https://doi.org/10.26685/urncst.211

Corsi, A., C. Bombieri, M.T. Valenti and M.G. Romanelli (2022). Tau isoforms: gaining insight into MAPT alternative splicing. Int. J. Mol. Sci. 23(23): 15383. https://doi.org/10.3390/ijms232315383

D'Alonzo, Z.J., V. Lam, R. Takechi, M. Nesbit, M. Vaccarezza and J.C. Mamo (2023). Peripheral metabolism of lipoprotein-amyloid beta as a risk factor for Alzheimer's disease: potential interactive effects of APOE genotype with dietary fats. Genes Nutr. 18(1): 2. https://doi.org/10.1186/s12263-023-00722-5

Dauar, M.T., A. Labonté, C. Picard, J. Miron, P. Rosa-Neto, H. Zetterberg, K. Blennow, S. Villeneuve and J. Poirier (2023). Characterization of the contactin 5 protein and its risk-associated polymorphic variant throughout the Alzheimer's disease spectrum. Alzheimers Dement. 19(7): 2816-2830. https://doi.org/10.1002/alz.12868

De Bertier, S., G. Lautrette, M.D. Amador, T. Miki, S. Boillée, C.S. Lobsiger, D. Bohl, F. Darios, S. Machat, M. Duchesne and P. Vourc'h (2025). MAPT mutations in amyotrophic lateral sclerosis: clinical, neuropathological and functional insights. J. Neurol. 272(4): 272. https://doi.org/10.1007/s00415-025-13007-1

Dong-Chen, X., C. Yong, X. Yang, S. Chen-Yu and P. Li-Hua (2023). Signaling pathways in Parkinson's disease: molecular mechanisms and therapeutic interventions. Signal Transduct. Target. Ther. 8(1): 73. https://doi.org/10.1038/s41392-023-01353-3

Ehn, E., J. Eisfeldt, J.M. Laffita-Mesa, H. Thonberg, J. Schoumans, A.M. Portaankorva, M. Viitanen, A. Lindstrand, I. Nennesemo and C. Graff (2025). A de novo, mosaic and complex chromosome 21 rearrangement causes APP triplication and familial autosomal dominant early ons*et al*zheimer disease. Sci. Rep. 15(1): 2912. https://doi.org/10.1038/s41598-025-86645-0

Firdaus, Z. and X. Li (2024). Unraveling the genetic landscape of neurological disorders: insights into pathogenesis, techniques for variant identification, and therapeutic approaches. Int. J. Mol. Sci. 25(4): 2320. https://doi.org/10.3390/ijms25042320

Gentile, G., V. La Cognata and S. Cavallaro (2021). The contribution of CNVs to the most common aging-related neurodegenerative diseases. Aging Clin. Exp. Res. 33(5): 1187-1195. https://doi.org/10.1007/s40520-020-01485-4

Giallongo, S., L. Longhitano, S. Denaro, S. D'Aprile, F. Torrisi, E. La Spina, C. Giallongo, G. Mannino, D. Lo Furno, A. Zappalà and R. Giuffrida (2022). The role of epigenetics in neuroinflammatory-driven diseases. Int. J. Mol. Sci. 23(23): 15218. https://doi.org/10.3390/ijms232315218

Grangeon, L., C. Charbonnier, A. Zarea, S. Rousseau, A. Rovelet-Lecrux, D. Bendetowicz, M. Lemaitre, C. Malrain, M. Quillard-Muraine, K. Cassinari and D. Maltete (2023). Phenotype and imaging features associated with APP duplications. Alzheimers Res. Ther. 15(1): 93. https://doi.org/10.1186/s13195-023-01172-2

Guo, P., C. Cao, Y. Ma and J. Wang (2021). Network-based analysis on genetic variants reveals the immunological mechanism underlying Alzheimer's disease. J. Neural Transm. 128(6): 803-816. https://doi.org/10.1007/s00702-021-02337-9

Hampel, H., J. Hardy, K. Blennow, C. Chen, G. Perry, S.H. Kim, V.L. Villemagne, P. Aisen, M. Vendruscolo, T. Iwatsubo and C.L. Masters (2021). The amyloid-β pathway in Alzheimer's disease. Mol. Psychiatry. 26(10): 5481-5503. https://doi.org/10.1038/s41380-021-01249-0

Hampel, H., Y. Hu, J. Hardy, K. Blennow, C. Chen, G. Perry, S.H. Kim, V.L. Villemagne, P. Aisen, M. Vendruscolo and T. Iwatsubo (2023). The amyloid-β pathway in Alzheimer's disease: a plain language summary. Neurodegener. Dis. Manag. 13(3): 141-149. https://doi.org/10.2217/nmt-2022-0037

Hoogmartens, J., R. Cacace and C. Van Broeckhoven (2021). Insight into the genetic etiology of Alzheimer's disease: a comprehensive review of the role of rare variants. Alzheimers Dement. Diagn. Assess. Dis. Monit. 13(1): e12155. https://doi.org/10.1002/dad2.12155

Ilieva, M. S. (2024). Non-coding RNAs in neurological and neuropsychiatric disorders: unraveling the hidden players in disease pathogenesis. Cells. 13(12): 1063. https://doi.org/10.3390/cells13121063

Koutsodendris, N., M.R. Nelson, A. Rao and Y. Huang (2022). Apolipoprotein E and Alzheimer's disease: findings, hypotheses, and potential mechanisms. Annu. Rev. Pathol. Mech. Dis. 17(1): 73-99. https://doi.org/10.1146/annurev-pathmechdis-030421-112756

Leitner, D., T. Kavanagh, E. Kanshin, K. Balcomb, G. Pires, M. Thierry, J.I. Suazo, J. Schneider, B. Ueberheide, E. Drummond and T. Wisniewski (2024). Differences in the cerebral amyloid angiopathy proteome in Alzheimer's disease and mild cognitive impairment. Acta Neuropathol. 148(1): 9. https://doi.org/10.1007/s00401-024-02767-1

Li, S., Z. Lei and T. Sun (2023). The role of microRNAs in neurodegenerative diseases: a review. Cell Biol. Toxicol. 39(1): 53-83. https://doi.org/10.1007/s10565-022-09761-x

López-Hernández, R., M.M. de la Torre-Álamo, B. García-Bueno, A. Baroja-Mazo, F.J. Fenoy and S. Cuevas (2025). Inflammasomes in Alzheimer's Progression: Nrf2 as a Preventive Target. Antioxidants. 14(2): 121. https://doi.org/10.3390/antiox14020121

Lui, M., S. Salamone, F. Pollastro, E. Mazzon and O. Artimagnella (2025). Cannabinerol restores mRNA splicing defects induced by β-amyloid in an in vitro model of Alzheimer's disease: a transcriptomic study. Int. J. Mol. Sci. 26(7): 3113. https://doi.org/10.3390/ijms26073113

Luo, Y.X., L.L. Yang and X.Q. Yao (2024). Gut microbiota-host lipid crosstalk in Alzheimer's disease: implications for disease progression and therapeutics. Mol. Neurodegener. 19(1): 35. https://doi.org/10.1186/s13024-024-00720-0

Maity, S., K. Farrell, S. Navabpour, S.N. Narayanan and T.J. Jarome (2021). Epigenetic mechanisms in memory and cognitive decline associated with aging and Alzheimer's disease. Int. J. Mol. Sci. 22(22): 12280. https://doi.org/10.3390/ijms222212280

Migliore, L. and F. Coppedè (2022). Gene-environment interactions in Alzheimer disease: the emerging role of epigenetics. Nat. Rev. Neurol. 18(11): 643-660. https://doi.org/10.1038/s41582-022-00714-w

Ming, C., M. Wang, Q. Wang, R. Neff, E. Wang, Q. Shen, J.S. Reddy, X. Wang, M. Allen, N. Ertekin-Taner and P.L. De Jager (2022). Whole genome sequencing-based copy number variations reveal novel pathways and targets in Alzheimer's disease. Alzheimers Dement. 18(10): 1846-1867. https://doi.org/10.1002/alz.12507

Murphy, J. and D.P. McKernan (2022). The effect of aggregated alpha synuclein on synaptic and axonal proteins in Parkinson's disease-a systematic review. Biomolecules. 12(9): 1199. https://doi.org/10.3390/biom12091199

Nehra, G., B. Bauer and A.M. Hartz (2022). Blood-brain barrier leakage in Alzheimer's disease: from discovery to clinical relevance. Pharmacol. Ther. 234: 108119. https://doi.org/10.1016/j.pharmthera.2022.108119

Nguyen, L.D., R.K. Chau and A.M. Krichevsky (2021). Small molecule drugs targeting non-coding RNAs as treatments for Alzheimer's disease and related dementias. Genes. 12(12): 2005. https://doi.org/10.3390/genes12122005

Nikom, D. and S. Zheng (2023). Alternative splicing in neurodegenerative disease and the promise of RNA therapies. Nat. Rev. Neurosci. 24(8): 457-

473. https://doi.org/10.1038/s41583-023-00717-6

Niu, R.Z., W.Q. Feng, L. Chen and T.H. Bao (2025). Single-cell transcriptomic profiling reveals regional differences in the prefrontal and entorhinal cortex of Alzheimer's disease brain. Int. J. Mol. Sci. 26(10): 4841. https://doi.org/10.3390/ijms26104841

Olufunmilayo, E.O. and R.D. Holsinger (2023). Roles of non-coding RNA in Alzheimer's disease pathophysiology. Int. J. Mol. Sci. 24(15): 12498. https://doi.org/10.3390/ijms241512498

Pan, L., L. Meng, M. He, *et al*. (2021). Tau in the pathophysiology of Parkinson's disease. J. Mol. Neurosci. 71: 2179-2191. https://doi.org/10.1007/s12031-020-01776-5

Paniri, A., M.M. Hosseini and H. Akhavan-Niaki (2024). Alzheimer's disease-related epigenetic changes: novel therapeutic targets. Mol. Neurobiol. 61(3): 1282-1317. https://doi.org/10.1007/s12035-023-03626-y

Ramakrishan, P., J. Rajangam, S.S. Mahinoor, S. Bisht, S. Mekala, D.K. Upadhyay, V.R. Solomon, G. Sabarees and R. Pelluri (2025). Unveiling the mTOR pathway modulation by SGLT2 inhibitors: a novel approach to Alzheimer's disease in type 2 diabetes. Metab. Brain Dis. 40(3): 1-30. https://doi.org/10.1007/s11011-025-01555-4

Rey, F., C. Pandini, L. Messa, R. Launi, B. Barzaghini, R. Zangaglia, M.T. Raimondi, S. Gagliardi, C. Cereda, G.V. Zuccotti and S. Carelli (2021). α-Synuclein antisense transcript SNCA-AS1 regulates synapses-and aging-related genes suggesting its implication in Parkinson's disease. Aging Cell. 20(12): e13504. https://doi.org/10.1111/acel.13504

Scholz, R., D. Brösamle, X. Yuan, M. Beyer and J.J. Neher (2024). Epigenetic control of microglial immune responses. Immunol. Rev. 323(1): 209-226. https://doi.org/10.1111/imr.13317

Sharma, M., P. Pal and S.K. Gupta (2024). Deciphering the role of miRNAs in Alzheimer's disease: predictive targeting and pathway modulation-a systematic review. Ageing Res. Rev. 102483. https://doi.org/10.1016/j.arr.2024.102483

Shi, Q., R.A. Gutierrez and M.A. Bhat (2025). Microglia, Trem2, and neurodegeneration. Neuroscientist. 31(2): 159-176. https://doi.org/10.1177/10738584241254118

Shobeiri, P., S. Alilou, M. Jaberinezhad, F. Zare, N. Karimi, S. Maleki, A.L. Teixeira, G. Perry and N. Rezaei (2023). Circulating long non-coding RNAs as novel diagnostic biomarkers for Alzheimer's disease (AD): a systematic review and meta-analysis. PLoS One. 18(3): e0281784. https://doi.org/10.1371/journal.pone.0281784

Shukla, A.K., P.S. Nilgirwar and S.D. Bali (2025). Current pharmacological treatments for neurodegenerative diseases. In: The Neurodegeneration Revolution. Academic Press. pp. 117-126. https://doi.org/10.1016/B978-0-443-28822-7.00005-2

Sinsky, J., K. Pichlerova and J. Hanes (2021). Tau protein interaction partners and their roles in Alzheimer's disease and other tauopathies. Int. J. Mol. Sci. 22(17): 9207. https://doi.org/10.3390/ijms22179207

Statello, L., C.J. Guo, L.L. Chen and M. Huarte (2021). Gene regulation by long non-coding RNAs and its biological functions. Nat. Rev. Mol. Cell Biol. 22(2): 96-118. https://doi.org/10.1038/s41580-020-00315-9

Sundram, S., N. Dhiman, R. Malviya and R. Awasthi (2024). Non-coding RNAs in regulation of protein aggregation and clearance pathways: current perspectives towards Alzheimer's research and therapy. Curr. Gene Ther. 24(1): 8-16. https://doi.org/10.2174/1566523223666230731093030

Thangavelu, L., E. Moglad, M. Afzal, W.H. Almalki, H. Malathi, P. Bansal, B. Rani, C. Walia, G.V. Sivaprasad, P. Rajput and M. Imran (2024). Non-coding RNAs in Parkinson's disease: regulating SNCA and alpha-synuclein aggregation. Pathol. Res. Pract. 261:155511. https://doi.org/10.1016/j.prp.2024.155511

Tiwari, P., R. Dwivedi, M. Kaushik, M. Tripathi and R. Dada (2025). Genetics and epigenetics of Alzheimer's disease: understanding pathogenesis and exploring therapeutic potential. J. Mol. Neurosci. 75(2): 1-5. https://doi.org/10.1007/s12031-025-02363-2

Waheed, Z., J. Choudhary, F.H. Jatala, Fatimah, A. Noor, I. Zerr and S. Zafar (2023). The role of tau proteoforms in health and disease. Mol. Neurobiol. 60(9): 5155-5166. https://doi.org/10.1007/s12035-023-03387-8

Wang, H., L.S. Wang, G. Schellenberg and W.P. Lee (2023). The role of structural variations in Alzheimer's disease and other neurodegenerative diseases. Front. Aging Neurosci. 14: 1073905. https://doi.org/10.3389/fnagi.2022.1073905

Wang, J., S. Lai, T. Zhou, Z. Xia, W. Li, W. Sha, J. Liu and Y. Chen (2022). Progranulin from different gliocytes in the nucleus accumbens exerts distinct roles in FTD-and neuroinflammation-induced depression-like behaviors. J. Neuroinflammation. 19(1): 318. https://doi.org/10.1186/s12974-022-02684-8

Wang, Y.R., X.Q. Zeng, J. Wang, C.J. Fowler, Q.X. Li, X.L. Bu, J. Doecke, P. Maruff, R.N. Martins, C.C. Rowe and C.L. Masters (2024). Autoantibodies to BACE1 promote Aβ accumulation and neurodegeneration in Alzheimer's disease. Acta Neuropathol. 148(1): 57. https://doi.org/10.1007/s00401-024-02814-x

Yang, C., Y. Li, C. Chen, Z. Sun, E. Liu, N. Wei, X. Liu, J. Shu, N. Zhao and M. Sun (2025). Long non-coding RNAs: crucial regulators in Alzheimer's disease pathogenesis and prospects for precision medicine. Mol. Neurobiol. 62(6): 7525-7541. https://doi.org/10.1007/s12035-025-04729-4

Zargaham, M.K., A. Ibrahim, M. Ahmed, M.M. Babar and J. Rajadas (2025). Targeting amyloidogenic proteins through cyclic peptides-a medicinal chemistry perspective. Bioorg. Med. Chem. 123: 118165. https://doi.org/10.1016/j.bmc.2025.118165.

Zhang, W., D. Xiao, Q. Mao and H. Xia (2023). Role of neuroinflammation in neurodegeneration development. Signal Transduct. Target. Ther. 8(1): 267. https://doi.org/10.1038/s41392-023-01486-5

Zhou, W., Y. Zhou, J. He, Y. Rao, P. Fei and J. Li (2023). TREM2 deficiency in microglia accelerates photoreceptor cell death and immune cell infiltration following retinal detachment. Cell Death Dis. 14(3): 219. https://doi.org/10.1038/s41419-023-05735-x.