IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

LEVERAGING BIOINFORMATICS FOR ALZHEIMER'S DISEASE: COMPUTATIONAL INSIGHTS INTO PATHOGENESIS AND BIOMARKER DISCOVERY

[1]Ananyaa Verma, [2]Dr. Prachi Srivastava

[1] Student, [2]Associate Professor

[1]Amity Institute of Biotechnology,

[1]Amity University, Lucknow, India

Abstract

Alzheimer's disease (AD), the leading cause of dementia, remains a major public health challenge. Despite extensive research, its complex genetic, molecular, and environmental underpinnings are not fully understood. This review highlights the role of bioinformatics in integrating and analyzing multi-dimensional datasets from genomics, transcriptomics, proteomics, and neuroimaging to advance AD research.

We outline core AD pathologies, including amyloid-beta plaques, tau tangles, and neuroinflammation, which drive neuronal dysfunction and cognitive decline. High-throughput genomic techniques, such as genome-wide association studies and next-generation sequencing, have identified key risk factors beyond the known. Transcriptomic methods, including bulk and single-cell RNA (Ribo Nucleic Acid) sequencing, reveal gene expression dynamics and cell-specific vulnerabilities.

Integrated bioinformatics approaches, such as network-based analyses, aid in biomarker discovery for early diagnosis and targeted therapy. Emerging technologies like spatial transcriptomics and multi-omics signal a promising future, reshaping AD research and advancing precision medicine.

Keywords: Alzheimer's Disease, Bioinformatics, Genomics, Transcriptomics, Biomarker Discovery, Precision Medicine

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia, affecting an estimated fifty-five million people worldwide and imposing a growing socioeconomic burden [1]. Clinically, AD manifests as progressive memory loss, cognitive decline, and behavioral changes, driven by amyloid-beta (Aβ) plaques, tau neurofibrillary tangles (NFTs), and chronic neuroinflammation [2]. The amyloid cascade hypothesis suggests Aβ aggregation disrupts neuronal function, triggering oxidative stress and inflammation, while

hyperphosphorylated tau exacerbates neuronal dysfunction [3]. Bioinformatics integrates multi-omics data to uncover disease mechanisms, with technologies like single-cell RNA sequencing offering insights into cellular heterogeneity and therapeutic targets [4][5].

2. Alzheimer's Disease: A Brief Overview

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that primarily affects cognitive functions, including memory, reasoning, and language. It is the leading cause of dementia worldwide, with an estimated fifty-five million people currently affected, a number expected to rise due to aging populations [1]. The disease is characterized by the accumulation of amyloid-beta (Aβ) plaques, neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein, neuroinflammation, and widespread neuronal loss, all contributing to synaptic dysfunction and brain atrophy [2]. Despite decades of research, AD remains an incurable disease, and current treatment options only provide symptomatic relief.

2.1 Pathophysiology and Molecular Mechanisms

The pathological hallmarks of AD include extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles (NFTs), both of which are considered central to disease onset and progression.

2.1.1 Amyloid Cascade Hypothesis

The amyloid hypothesis suggests that abnormal processing of amyloid precursor protein (APP) leads to the formation of toxic Aβ species, which aggregate to form plaques [6]. APP is cleaved by β-secretase and γ-secretase, generating Aβ peptides, primarily Aβ42 and Aβ40. The Aβ42 species is particularly prone to aggregation and forms insoluble fibrils that accumulate in the extracellular space, disrupting synaptic function [3]. These plaques trigger a cascade of neurotoxic events, including oxidative stress, neuroinflammation, and neuronal apoptosis, which ultimately lead to cognitive decline [7].

2.1.2 Tau Pathology and Neurofibrillary Tangles

In parallel with Aβ deposition, tau protein undergoes hyperphosphorylation, leading to the formation of NFTs. Tau is a microtubule-associated protein essential for stabilizing neuronal cytoskeletons. However, hyperphosphorylation reduces tau's ability to bind microtubules, causing it to aggregate into paired helical filaments (PHFs) and NFTs [8]. These aggregates impair axonal transport, leading to synaptic dysfunction and neuronal death. Studies suggest that tau pathology spreads in a prion-like manner, propagating from affected to healthy neurons [9].

2.1.3 Neuroinflammation and Glial Activation

Neuroinflammation is another critical aspect of AD pathology. Microglia and astrocytes become chronically activated in response to Aβ plaques and NFTs, releasing pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 [10]. While initially beneficial in clearing debris, prolonged glial activation contributes to synaptic loss, neuronal damage, and blood-brain barrier dysfunction [11]. Genetic studies have identified variants in immune-related genes, such as TREM2, highlighting the role of innate immunity in AD progression [12].

2.1.4 Mitochondrial Dysfunction and Oxidative Stress

Mitochondrial dysfunction is also implicated in AD, as impaired energy metabolism and increased reactive oxygen species (ROS) production leads to neuronal damage [13]. Aβ peptides have been shown to localize within mitochondria, impairing electron transport chain (ETC) function and promoting apoptosis [14]. Oxidative stress further exacerbates tau pathology, contributing to neurodegeneration [15].

2.2 Genetic and Environmental Risk Factors

2.2.1 Genetic Factors

AD has both sporadic and familial forms, with genetic predisposition playing a crucial role in disease susceptibility.

- Early-Onset Familial AD (EOFAD): Mutations in APP, PSEN1, and PSEN2 genes account for less than 5% of cases but lead to an aggressive form of the disease, typically manifesting before the age of sixty-five [16].
- Late-Onset AD (LOAD): The apolipoprotein E (APOE) ε4 allele is the strongest genetic risk factor for LOAD, increasing the likelihood of developing AD by threefold in heterozygous carriers and up to fifteenfold in homozygous individuals [17].
- Other Risk Genes: Genome-wide association studies (GWAS) have identified additional risk loci, including CLU, PICALM, BIN1, and TREM2, which are involved in lipid metabolism, synaptic function, and immune response. [12][18]

2.2.2 Environmental and Lifestyle Factors

Apart from genetic predisposition, various environmental and lifestyle factors contribute to AD risk.

- Hypertension, diabetes, and hypercholesterolemia increase the likelihood of developing AD by promoting vascular dysfunction and chronic inflammation [1].
- A Mediterranean diet rich in antioxidants and regular physical activity have been associated with reduced AD risk. [19]
- Lifelong learning and social interactions contribute to cognitive reserve, potentially delaying the onset of AD symptoms. [20]

2.3 Current Challenges in Diagnosis and Treatment

2.3.1 Diagnostic Challenges

AD diagnosis remains a significant challenge due to its insidious onset and symptom overlap with other dementias. Current diagnostic approaches include:

- Neuroimaging: MRI and PET scans detect structural and functional changes in the brain, but their accessibility is limited due to cost.
- CSF Biomarkers: Abnormal levels of Aβ42, total tau (t-tau), and phosphorylated tau (p-tau) are indicative of AD but require invasive lumbar punctures. [21]
- Blood Biomarkers: Emerging research on plasma p-tau and neurofilament light chain (NfL) shows promise for non-invasive diagnosis. [22]

2.3.2 Treatment Limitations

Current FDA-approved treatments, such as cholinesterase inhibitors (donepezil, rivastigmine) and NMDA receptor antagonists (memantine), offer symptomatic relief but do not alter disease progression. Recent monoclonal antibody therapies targeting Aβ, such as aducanumab and lecanemab, show potential in slowing cognitive decline but face controversy regarding their efficacy and safety. [23]

3. Bioinformatics in Alzheimer's Disease Research

Bioinformatics has emerged as a transformative discipline in Alzheimer's disease (AD) research, enabling the systematic integration and analysis of complex, heterogeneous datasets. By applying advanced computational methods to genomic, transcriptomic, proteomic, and neuroimaging data, researchers are uncovering novel insights into AD pathogenesis, identifying potential biomarkers, and developing predictive models that may ultimately guide personalized therapeutic strategies.

3.1 Integration of Multi-Omics Data

High-throughput technologies have generated vast datasets spanning multiple layers of biological information. Integrative multi-omics approaches combine data from genomics, transcriptomics, proteomics, and metabolomics to construct a comprehensive view of the molecular landscape in AD. For example, integrated analyses have demonstrated that disturbances in lipid metabolism, inflammatory responses, and synaptic signalling converge to drive AD pathology. [24] This systems-level perspective not only facilitates the discovery of novel biomarkers but also helps to elucidate regulatory networks and molecular pathways that are disrupted during disease progression.

3.2 Bioinformatics Tools and Resources

A wide range of specialized computational tools and databases have been developed to support AD research:

- Data Repositories:
  - The Alzheimer's Disease Neuroimaging Initiative (ADNI) provides standardized datasets comprising neuroimaging, cerebrospinal fluid (CSF) biomarkers, and longitudinal clinical assessments. [21][25]
  - Public repositories such as the Gene Expression Omnibus (GEO) and the AlzGene database offer access to gene expression profiles and genetic association data relevant to AD.
- Analytical Platforms:
  - Software such as Cytoscape enables the visualization and analysis of complex biomolecular networks, while Ingenuity Pathway Analysis (IPA) and similar platforms facilitate pathway enrichment studies. [7]
  - Customized bioinformatics pipelines allow researchers to perform differential expression analysis, identify co-expression networks, and predict protein–protein interactions that underlie AD pathology.

These resources have significantly accelerated the pace at which researchers can generate and test hypotheses about the molecular drivers of AD.

3.3 Machine Learning and Predictive Analytics

The incorporation of machine learning (ML) and artificial intelligence (AI) techniques has further propelled AD research. ML algorithms—including support vector machines, random forests, and deep learning networks—are increasingly used to analyze large-scale datasets from neuroimaging and omics studies. Recent applications include the following:

- Early Diagnosis and Patient Stratification: Advanced ML models have been developed to differentiate between AD patients and cognitively normal individuals by extracting features from MRI, PET scans, and genetic data. For instance, studies have shown that ML-based classification methods can achieve high accuracy in predicting disease onset and progression. [26]

- Predictive Modelling: Predictive analytics that integrate multi-modal data have been used to stratify patients based on risk factors and to forecast disease trajectories. These models are essential for advancing precision medicine, as they help to identify individuals who may benefit from early interventions. [27]

3.4 Neuroinformatics and Imaging Data Analysis

Neuroinformatics focuses on the acquisition, storage, and computational analysis of neuroimaging data. Techniques such as voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) provide detailed information about brain structure and connectivity changes in AD. Computational algorithms process these imaging datasets to detect subtle morphological alterations that may precede clinical symptoms. When combined with molecular data, neuroimaging analytics offer a powerful means to correlate brain structural changes with underlying genetic and transcriptomic alterations. [27] This integrative approach enhances our understanding of the spatial distribution of neurodegeneration and its association with molecular pathology.

3.5 Emerging Trends: Single-Cell Sequencing and Network Biology

Recent advancements in single-cell sequencing have provided unprecedented insights into the cellular heterogeneity of the AD brain. Single-cell transcriptomic studies have revealed distinct cell populations and uncovered cell-type-specific gene expression changes linked to AD pathology. [28] These findings are crucial for understanding how individual cell types contribute to disease progression and for identifying novel therapeutic targets.

In parallel, network biology approaches are being used to construct and analyze gene co-expression and protein–protein interaction networks. Such network models help pinpoint key regulatory nodes or “hubs” that may represent critical points of intervention. The integration of single-cell data with network analysis is particularly promising for revealing the complex interplay between different cell types and molecular pathways in AD. [24]

4. Genomic and Transcriptomic Approaches

High-throughput genomic and transcriptomic technologies have transformed Alzheimer’s disease (AD) research by providing insights into the genetic architecture and dynamic gene expression patterns underlying the disease. In this section, we review key methodologies and findings from genomic and transcriptomic studies, discuss how integrated analyses have advanced our understanding of AD pathogenesis, and highlight current challenges and emerging technologies in the field.

4.1 Genomic Approaches in Alzheimer’s Disease

4.1.1 Genome-Wide Association Studies (GWAS) and Next-Generation Sequencing

Genome-wide association studies (GWAS) have identified numerous common variants that modestly increase the risk for late-onset AD. Early GWAS highlighted the apolipoprotein E (APOE) ε4 allele as the strongest genetic risk factor; subsequent large-scale meta-analyses have revealed additional susceptibility loci including CLU, PICALM, BIN1, and TREM2, among others. [29] These studies implicate diverse biological pathways such as amyloid-beta (Aβ) processing, lipid metabolism, synaptic function, and immune regulation.

Next-generation sequencing (NGS) techniques, including whole-exome sequencing (WES) and whole-genome sequencing (WGS), have further expanded our knowledge by uncovering rare and novel variants in both familial and sporadic AD cases. For example, rare mutations in APP, PSEN1, and PSEN2 are well-established causes of early-onset familial AD. In addition, the development of polygenic risk scores, which combine the effects of multiple common variants, is emerging as a tool to estimate an individual’s genetic risk and to elucidate the cumulative contribution of low-effect-size alleles. [30]

4.1.2 Functional Genomics and Epigenetic Modifiers

Beyond DNA sequence variation, functional genomic approaches—including the study of non-coding RNAs and epigenetic modifications—are providing further insights into AD. Although not the primary focus of this section, it is important to note that alterations in DNA methylation and histone modifications are being investigated for their roles in modulating gene expression in AD. These studies, in combination with GWAS, are beginning to identify regulatory elements that could link genetic risk with altered neuronal function.

4.2 Transcriptomic Approaches in Alzheimer's Disease

4.2.1 Bulk RNA Sequencing

Bulk RNA sequencing (RNA-seq) has been instrumental in characterizing differential gene expression between AD and non-AD brain tissues. Analyses of homogenized brain samples from regions such as the hippocampus, prefrontal cortex, and temporal lobe have consistently revealed dysregulation in genes involved in synaptic transmission, neuroinflammation, mitochondrial function, and cellular stress responses. [31] These studies provide a broad snapshot of the transcriptional alterations associated with AD but are limited by tissue heterogeneity.

4.2.2 Single-Cell and Single-Nucleus RNA Sequencing

To overcome the limitations of bulk analysis, single-cell RNA sequencing (scRNA-seq) and single-nucleus RNA sequencing (snRNA-seq) have been employed to resolve cell-type-specific gene expression patterns. These high-resolution approaches have identified distinct subpopulations of neurons, astrocytes, oligodendrocytes, and microglia with unique transcriptional signatures in the AD brain. [28] Such studies have revealed, for instance, that specific microglial subsets may play a critical role in the inflammatory response, while certain neuronal populations exhibit vulnerability to degeneration. These insights are crucial for understanding the cellular heterogeneity of AD pathology and for identifying cell-specific therapeutic targets.

4.3 Integration of Genomic and Transcriptomic Data

4.3.1 Network Analysis and Systems Biology

Network-based methodologies, such as Weighted Gene Co-expression Network Analysis (WGCNA), have been used to cluster genes into modules based on their co-expression patterns. These gene networks are then correlated with clinical and pathological traits to identify modules that are most relevant to AD progression. [32] Such systems biology approaches not only highlight key regulatory hubs but also offer insights into how disturbances in specific pathways (e.g., inflammation, synaptic signalling) contribute to the multifactorial nature of AD.

4.4 Challenges and Future Directions

4.4.1 Addressing Sample Heterogeneity and Temporal Dynamics

One of the primary challenges in both genomic and transcriptomic studies is the intrinsic heterogeneity of brain tissues. Variability in cell-type composition and differences in the stages of disease progression can obscure true molecular signals. Future studies are increasingly focusing on longitudinal designs and region-specific sampling to capture the dynamic progression of AD. Additionally, the integration of spatial transcriptomics—which retains the anatomical context of gene expression—promises to further enhance our understanding of AD pathology. [33]

Conclusion

The review has explored the multifaceted role of bioinformatics in advancing our understanding of Alzheimer's disease (AD). By examining the fundamental pathological mechanisms—from the amyloid cascade and tau pathology to neuroinflammation and mitochondrial dysfunction—we established a comprehensive framework for understanding the disease's etiology. The subsequent sections highlighted how bioinformatics approaches have revolutionized AD research by enabling the integration of diverse datasets, including genomic, transcriptomic, and neuroimaging information.

The application of genomic technologies, particularly genome-wide association studies (GWAS) and next-generation sequencing, has not only reinforced the significance of established risk factors like the APOE ε4 allele but also uncovered novel loci such as CLU, PICALM, BIN1, and TREM2. These discoveries underscore the complex genetic architecture underlying AD and highlight the multifactorial nature of the disease. Furthermore, transcriptomic analyses—ranging from bulk RNA sequencing to high-resolution single-cell RNA sequencing—have elucidated the dynamic gene expression changes that occur in various brain regions and cell types during AD progression. Such studies have been critical in revealing cell-specific vulnerabilities and in mapping the transcriptional networks that drive neurodegeneration.

Integrative approaches, such as expression quantitative trait loci (eQTL) mapping and network analysis, have further bridged the gap between genetic predisposition and functional gene expression, providing a systems-level perspective on AD pathology. These methodologies not only facilitate the identification of candidate biomarkers for early diagnosis but also offer promising avenues for targeted therapeutic interventions.

Despite these advances, challenges remain, particularly in addressing sample heterogeneity and in developing robust, interpretable computational models. Future research must continue to refine data integration techniques and harness emerging technologies such as spatial transcriptomics and multi-omics approaches to further unravel the complexities of AD.

In conclusion, the convergence of bioinformatics, genomics, and transcriptomics is paving the way for transformative insights into Alzheimer's disease. This integrative approach holds significant promise for the development of precision medicine strategies that may one day enable early detection and personalized treatment, ultimately improving patient outcomes in the battle against AD.

Acknowledgment

The authors sincerely thank Amity University for providing the necessary resources and support for this research. Special appreciation is extended to Dr. Prachi Srivastava for her invaluable guidance, mentorship, and insightful discussions that greatly contributed to this study.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

References

[1] Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., ... & Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. The Lancet, 396(10248), 413-446.

[2] Hardy, J., & Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. Science, 297(5580), 353-356.

[3] Selkoe, D. J., & Hardy, J. (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Molecular Medicine, 8(6), 595-608.

[4] Zhang, B., Gaiteri, C., Bodea, L. G., Wang, Z., McElwee, J., Podtelezhnikov, A. A., ... & Schadt, E. E. (2013). Integrated systems approach identifies genetic nodes and networks in late-onset Alzheimer's disease. Cell, 153(3), 707-720.

[5] Mathys, H., Davila-Velderrain, J., Peng, Z., Gao, F., Mohammadi, S., Young, J. Z., ... & Teichmann, S. A. (2019). Single-cell transcriptomic analysis of Alzheimer's disease. Nature, 570(7761), 332-337.

[6] Hardy, J., & Higgins, G. A. (1992). Alzheimer's disease: the amyloid cascade hypothesis. Science, 256(5054), 184-185.

[7] De Strooper, B., & Karran, E. (2016). The cellular phase of Alzheimer's disease. Cell, 164(4), 603-615.

[8] Wang, Y., & Mandelkow, E. (2016). Tau in physiology and pathology. Nature Reviews Neuroscience, 17(1), 5-21.

[9] Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. Acta Neuropathologica, 82(4), 239-259.

[10] Heneka, M. T., Carson, M. J., El Khoury, J., Landreth, G. E., Brosseron, F., Feinstein, D. L., ... & Kummer, M. P. (2015). Neuroinflammation in Alzheimer's disease. The Lancet Neurology, 14(4), 388-405.

[11] Hansen, D. V., Hanson, J. E., & Sheng, M. (2018). Microglia in Alzheimer's disease. The Journal of Cell Biology, 217(2), 459-472.

[12] Guerreiro, R., Wojtas, A., Bras, J., Carrasquillo, M., Rogaeva, E., Majounie, E., ... & Hardy, J. (2013). TREM2 variants in Alzheimer's disease. New England Journal of Medicine, 368(2), 117-127.

[13] Reddy, P. H., & Beal, M. F. (2008). Amyloid beta, mitochondrial dysfunction and synaptic damage: Implications for cognitive decline in aging and Alzheimer's disease. Trends in Molecular Medicine, 14(2), 45-53.

[14] Wang, Y., Sun, Y., Sun, L., & Zheng, H. (2020). Mitochondrial dysfunction and oxidative stress in Alzheimer's disease. Free Radical Biology and Medicine, 150, 160-173.

[15] Zhao, Y., & Zhao, B. (2013). Oxidative stress and the pathogenesis of Alzheimer's disease. Oxidative Medicine and Cellular Longevity, 2013, 316523.

[16] Bekris, L. M., Yu, C. E., Bird, T. D., & Tsuang, D. W. (2010). Genetics of Alzheimer disease. Journal of Geriatric Psychiatry and Neurology, 23(4), 213-227.

[17] Liu, C. C., Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: Risk, mechanisms, and therapy. Nature Reviews Neurology, 9(2), 106-118.

[18] Harold, D., Abraham, R., Hollingworth, P., Sims, R., Gerrish, A., Hamshere, M. L., ... & Williams, J. (2009). Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nature Genetics, 41(10), 1088-1093.

[19] Scarmeas, N., Anastasiou, C. A., & Yannakoulia, M. (2018). Nutrition and prevention of cognitive impairment. The Lancet Neurology, 17(11), 1006-1015.

[20] Stern, Y. (2009). Cognitive reserve. Neuropsychologia, 47(10), 2015-2028.

[21] Jack, C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., ... & Sperling, R. (2018). NIA-AA research framework: Toward a biological definition of Alzheimer's disease. Alzheimer's & Dementia, 14(4), 535-562.

[22] Mattsson-Carlgren, N., Andersson, E., Janelidze, S., Ossenkoppele, R., Insel, P., & Zetterberg, H. (2020). Aβ deposition is associated with increased tau accumulation independently of tau isoform. Neuron, 107(6), 967-975.

[23] Van Dyck, C. H., Swanson, C. J., Aisen, P., Bateman, R. J., Chen, C., Gee, M., ... & Siemers, E. (2023). Lecanemab in early Alzheimer's disease. New England Journal of Medicine, 388(1), 9-21.

[24] Wang, M., Beckmann, N. D., Roussos, P., Wang, E., Zhou, X., Wang, Q., ... & Zhang, B. (2016). Integrative network analysis of nineteen brain regions identifies molecular signatures and networks underlying Alzheimer's disease. Genome Medicine, 8(1), 104.

[25] Weiner, M. W., Veitch, D. P., Aisen, P. S., Beckett, L. A., Cairns, N. J., Green, R. C., ... & Trojanowski, J. Q. (2017). The Alzheimer's Disease Neuroimaging Initiative 3: Continued innovation for clinical trial improvement. Alzheimer's & Dementia, 13(5), 561-571.

[26] Rathore, S., Habes, M., Iftikhar, M. A., Shacklett, A., & Davatzikos, C. (2017). A review on neuroimaging-based classification studies and associated feature extraction methods for Alzheimer's disease and its prodromal stages. NeuroImage, 155, 530-548.

[27] Arbabshirani, M. R., Plis, S., Sui, J., & Calhoun, V. D. (2017). Single subject prediction of brain disorders in neuroimaging: Promises and pitfalls. NeuroImage, 145, 137-165.

[28] Mathys, H., Davila-Velderrain, J., Peng, Z., Gao, F., Mohammadi, S., Young, J. Z., ... & Teichmann, S. A. (2019). Single-cell transcriptomic analysis of Alzheimer's disease. Nature, 570(7761), 332-337.

[29] Kunkle, B. W., Grenier-Boley, B., Sims, R., Bis, J. C., Damotte, V., Naj, A. C., … & Lambert, J. C. (2019). Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity, and lipid processing. Nature Genetics, 51(3), 414-430.

[30] Naj, A. C., Jun, G., Beecham, G. W., Wang, L. S., Vardarajan, B. N., Buros, J., … & Schellenberg, G. D. (2011). Common variants at MS4A4/MS4A6E, CD2AP, CD33, and EPHA1 are associated with late-onset Alzheimer's disease. Nature Genetics, 43(5), 436-441.

[31] Mostafavi, S., Gaiteri, C., Sullivan, S. E., White, C. C., Tasaki, S., Xu, J., … & De Jager, P. L. (2018). A molecular network of the aging human brain provides insights into the pathology and cognitive decline of Alzheimer's disease. Nature Neuroscience, 21(6), 811-819.

[32] Langfelder, P., & Horvath, S. (2008). WGCNA: An R package for weighted correlation network analysis. BMC Bioinformatics, 9, 559.

[33] Ståhl, P. L., Salmén, F., Vickovic, S., Lundmark, A., Navarro, J. F., Magnusson, J., … & Lundeberg, J. (2016). Visualization and analysis of gene expression in tissue sections by spatial transcriptomics. Science, 353(6294), 78-82.