The Functional Role of Alzheimer Risk Loci in Disease Progression

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Understanding the regulatory mechanisms that drive Alzheimer's disease (AD) is critical for translating genetic risk into possible therapeutics. This review of a study published in Cell by Xiong et al. provides a comprehensive, cell-type-specific analysis of the AD brain's epigenomic and transcriptional landscape, offering a foundational framework for interpreting noncoding genetic variants. By linking regulatory elements to gene expression through multimodal single-nucleus sequencing, the work highlights how disruptions in chromatin accessibility contribute to disease progression and cellular identity loss. Its significance lies not just in the findings, but in its broader impact, which is demonstrating how integrative, high-resolution approaches can uncover the regulatory circuitry underlying neurodegeneration. This has profound implications for precision medicine, as it enables researchers to move beyond association studies and toward mechanistic models of AD that can inform targeted therapies. The study also raises essential questions about the role of epigenomic erosion in neuronal decline, pointing to chromatin-modifying enzymes and regulatory instability as potential intervention points. Ultimately, this research shifts the focus from static genetic risk to dynamic regulatory dysfunction, setting the stage for systems-level exploration of complex brain diseases.

Introduction

Epigenetics, a rapidly evolving field, explores the dynamic layer of gene regulation that operates without altering the underlying DNA sequence. This field of study has unveiled how environmental factors, lifestyle choices, and even aging can shape the way genes are expressed. Central to epigenetics are epigenomic modifications, such as DNA methylation, histone modification, and chromatin remodeling, which are crucial for maintaining cellular identity and proper function. For example, DNA methylation is used to silence unnecessary genes for specific cell types, such as how neurons silence glial-specific genes. Over time, however, the epigenome may lose its integrity through a process known as epigenomic erosion, where these epigenetic regulatory mechanisms falter due to environmental and internal factors. This phenomenon has been linked to various age-related conditions and diseases, such as Parkinson's disease and Huntington's disease, but most notably Alzheimer's disease (AD), a neurodegenerative disorder that affects millions of elderly individuals worldwide.

Alzheimer's disease is marked by progressive cognitive decline, memory loss, and structural changes in the brain, such as the accumulation of amyloid plaques and tau tangles. Amyloid plaques are formed from Amyloid precursor proteins. These proteins are cleaved in a normal process, however, in Alzheimer's pathology, the proteins are cleaved at lengths resulting in Aβ42 (amyloid-beta 42) peptides, which aggregate and form oligomers. Oligomers combine to form fibrils and eventually extracellular amyloid plaques, acting as physical barriers between neurons. On the other hand, Tau tangles are formed when the tau protein becomes excessively phosphorylated and hinders its purpose to bind to microtubules. These unbound tau proteins self-associate into oligomers, leading to neurofibrillary tangle aggregates that greatly impact neuronal function and may lead to the death of neurons. While the hallmarks of AD have been well-documented, its underlying molecular mechanisms remain unclear. Emerging research

points to a significant role of epigenetic dysregulation in the onset and progression of the disease. Studies have identified abnormal DNA methylation patterns, histone modifications, and chromatin structure changes in the brains of individuals with AD. Epigenomic erosion is influenced heavily by age, and in later years, global DNA hypomethylation with specific genes showing hypermethylation, loss of histone modification balance, and accumulation of non-coding RNAs make neurons more vulnerable to pathological processes. For example, hypomethylation can lead to the overexpression of the amyloid precursor protein, which in turn forms amyloid plaques. These findings suggest that epigenomic erosion may not only accompany but actively contribute to the development of the disorder.

The implications of these discoveries extend far beyond the laboratory. Alzheimer's disease presents an urgent public health challenge, with rising prevalence due to increasing life expectancy, predicted to increase by nearly 5 years in 2050 (1). By investigating AD on the molecular level, particularly through the lens of epigenetics, researchers hope to uncover novel therapeutic strategies, such as the creation of epigenetic drugs, which include DNA methylation modulators and histone deacetylase inhibitors. Targeting epigenetic mechanisms could offer innovative approaches to delay or even prevent disease progression, improving the quality of life for millions and reducing the societal and economic burden associated with AD care.

This paper delves into a study published in Cell by Xiong et al. about the role of specific non-coding loci in the progression of Alzheimer's Disease (2). By examining how epigenomic erosion contributes to the development of AD, this research summary seeks to highlight the potential for new epigenetic-based interventions. Furthermore, it underscores the importance of integrating molecular insights into the development of treatments, offering hope for breakthroughs.

Epigenomic erosion, which is a gradual loss of epigenetic regulation that can disrupt gene expression patterns over time, was prominent in non-coding loci at risk of Alzheimer's throughout disease progression. While GWAS studies have identified non-coding loci linked to AD, their functional impact is often mediated by epigenetic mechanisms that control chromatin structure and transcriptional activity. Epigenomic erosion, characterized by changes such as DNA hypomethylation and histone modifications, may amplify the dysregulation of key AD-associated genes, further exacerbating neuroinflammation, amyloid-beta accumulation, and tau pathology. By exploring how epigenomic instability interacts with these non-coding loci, researchers can better understand the molecular underpinnings of AD and identify novel therapeutic targets aimed at restoring proper gene regulation.

Research Question

Recent genome-wide association studies (GWAS) have identified numerous non-coding loci associated with Alzheimer's disease (AD) risk, shedding light on the complex genetic structure underlying the disease. These non-coding regions, which do not encode proteins, are thought to regulate gene expression through mechanisms such as enhancer activity, promoter regulation, chromatin remodeling, and interactions with transcription factors. For example, non-coding risk loci near the BIN1 gene (a known AD susceptibility gene) are believed to act as enhancers, regulating BIN1 expression in microglia. Dysregulated enhancer activity could result in abnormal

BIN1 expression, potentially causing neuroinflammation which is implicated in AD. Furthermore, non-coding loci often harbor regulatory elements that control the timing, location, and level of gene expression. In AD, these loci may regulate genes involved in neuroinflammation, amyloid-beta production, tau phosphorylation, and synaptic integrity, which are hallmarks of the disease. For instance, regulatory elements within non-coding regions could interact with transcription factors, proteins that control gene expression by binding to DNA, like PU.1 and NF-κB, which are highly active in microglia and astrocytes, key immune cells involved in AD. Furthermore, epigenetic modifications in these loci, such as DNA methylation and histone acetylation, may influence chromatin accessibility and transcriptional output. Despite these findings, the full spectrum of functional roles of these loci remains poorly understood, posing a significant barrier to translating genetic associations into biological insights and therapeutic medicines. Understanding how these loci influence AD transcriptional regulatory circuitry is critical to uncovering the molecular pathways driving disease progression.

Emerging technologies, such as single-cell transcriptomics, CRISPR-based functional screens, and Hi-C chromatin interaction mapping, provide newfound methods to explore the interactions between non-coding loci and transcriptional regulatory networks in a cell-type-specific manner. This research investigates the role of non-coding loci in Alzheimer's disease by employing brain regulome mapping, multimodal integration, and peak-to-gene linking to uncover regulatory modules. By enhancing our molecular understanding of Alzheimer's pathogenesis, this study identifies potential targets for early diagnosis and therapeutic intervention.

Advancements in high-resolution genomic technologies have revolutionized the study of Alzheimer's disease by enabling researchers to dissect the intricate relationship between non-coding loci and transcriptional regulation at an unprecedented scale. By leveraging techniques such as single-cell transcriptomics and chromatin interaction mapping, scientists can now investigate how regulatory elements shape gene expression within specific brain cell types. This study applies these cutting-edge approaches to map the brain regulome, integrating multimodal datasets to identify key regulatory modules that may contribute to AD pathogenesis. Through this framework, researchers aim to bridge the gap between genetic risk factors and functional consequences, paving the way for improved diagnostic and therapeutic strategies.

Findings

This study analyzed post-mortem human brain prefrontal cortex samples from 92 individuals enrolled in the Religious Order Study (ROS) and the Rush Memory and Aging Project (MAP), comprising individuals with Alzheimer's Disease (AD) at varying stages and age-matched controls. The researchers performed single-nucleus RNA sequencing (snRNA-seq) and chromatin accessibility profiling (snATAC-seq), producing 414,964 high-quality transcriptomes and 171,000 epigenomes after applying strict quality control measures. This comprehensive dataset allowed for an in-depth investigation of the epigenomic and transcriptomic landscapes of brain cells and their potential roles in AD.

The study grouped the individuals into non-AD controls (n=48), early-stage AD (n=29), and late-stage AD (n=15) based on seven clinico-pathological measurements. Using snRNA-seq, the researchers profiled 414,964 single cells, identifying seven major brain cell types: excitatory

neurons (22,000 cells), inhibitory neurons (21,000 cells), oligodendrocytes (101,000 cells), astrocytes (10,000 cells), oligodendrocyte progenitor cells (OPCs) (7,200 cells), microglia (8,600 cells), and vascular cells (1,200 cells). The data also allowed for the identification of 14 excitatory subtypes, 25 inhibitory subtypes, and 22 glial and vascular subtypes, giving a detailed view of the heterogeneity within brain cell populations. For the snATAC-seq, the profiling of chromatin accessibility across these cell types revealed 367,242 unique ATAC peaks, with the peak count ranging from 80,000 to 200,000 per cell type, except for vascular cells, which had fewer peaks due to their lower cell number.

The cell-type-specific ATAC peaks were linked to functional pathways specific to each cell type. For example, synaptic signaling was enriched in neurons, axon ensheathment was observed in oligodendrocytes, and extracellular matrix organization was prominent in pericytes and endothelial cells. The study identified 130,193 peaks with cell-type specificity, confirming the relationship between chromatin accessibility and gene expression in these cells. This correlation between chromatin accessibility and gene expression helped the researchers identify potential transcription factor (TF) regulators that may influence brain cell identity and contribute to AD. Using chromVar, the researchers identified 44 high-confidence TF regulators that showed strong correlations between TF enrichment and ATAC-inferred gene expression, with key TFs such as NEUROD2/D6, MEF2C, and EGR family TFs in excitatory neurons, STAT4 in inhibitory neurons, and SPI1/B, and IRF5/8 in microglia.

Further investigation of chromatin accessibility and transcriptional regulation using a snRNA-snATAC integration framework helped the researchers resolve intra-cell heterogeneity within each major cell type. By integrating RNA and ATAC data, the study generated high-resolution subtype annotations and built a joint cell-cell graph that allowed for the identification of peak-to-gene links and the prediction of regulatory relationships between distal peaks and gene expression. The integration method demonstrated improved alignment between RNA and ATAC profiles compared to other existing integration methods, like scGLUE and Seurat. By building peak-to-gene links and using regression models, the researchers were able to classify high-confidence peak-to-gene relationships, revealing that many regulatory regions are involved in gene expression coordination across different brain cell types.

The study also explored the genetic basis of AD by analyzing the heritability enrichment of AD-associated genetic variants in the ATAC peaks of different brain cell types. Microglia-specific peaks were found to be strongly enriched for AD heritability, while other cell types and shared peaks (those present in more than five cell types) showed no significant enrichment. By focusing on microglia, the researchers discovered that peaks containing TF binding sites (TFBS) for important microglial regulators like SPI1 and RUNX1 were particularly enriched for AD risk loci, highlighting the regulatory roles these TFs play in AD pathogenesis. The study also identified several AD-associated genetic variants, including rs9648346, which was predicted to affect the expression of JAZF1 in microglia, and rs867611, which was linked to PICALM, an established AD risk gene. These findings underscore the importance of microglia in the epigenomic landscape of AD and the potential for identifying novel therapeutic targets through the investigation of regulatory networks within these cells.

Overall, the study provides a detailed, multi-layered map of brain cell epigenomes and transcriptomes, with a focus on identifying the regulatory networks that contribute to AD. The results highlight the importance of microglia and their regulatory pathways in AD risk, offering insights into potential therapeutic strategies targeting the epigenomic landscape of brain cells.

The study continued by prioritizing Alzheimer's Disease (AD) genome-wide association study (GWAS) variants based on epigenomic annotations and peak-to-gene links. A significant finding was the overlap of AD GWAS variants with cell-type-specific chromatin peaks. The majority of these variants (18 out of 19 loci) overlapped microglial peaks, with smaller overlaps in astrocytes and excitatory neurons. Three loci were exclusively found in microglia, including those near microglial transcription factor (TF) SPI1 and myeloid receptors TREM2/TREML2, while 8 loci appeared in multiple cell types, including well-known AD risk genes such as BIN1, CLU, and APP.

To prioritize functional AD-GWAS variants for each locus, the researchers used peak-to-gene links along with genetic evidence such as expression quantitative trait loci (eQTLs) and physical interactions from HiChIP and PLAC-seq. They identified eight genes specifically prioritized in microglia, including PICALM, SCIMP, and JAZF1, and several genes prioritized in multiple cell types. Of particular note were three genes that were potentially downstream targets of AD-GWAS loci, including KANSL1-AS1, ACE, and CARF. Among the prioritized variants, 12 of 19 were found within TF motifs, suggesting that these variants may disrupt microglial-specific regulatory networks. For example, rs9648346, located in the JAZF1 locus, disrupts an SPI1 binding site in microglia and is supported by microglia-specific eQTLs and PLAC-seq data. This variant is linked to the regulation of JAZF1, a gene involved in glucose production and tau phosphorylation, processes implicated in AD. Similarly, the lead variant for the PICALM locus, rs867611, was identified as a microglial regulator, supported by single-cell eQTL and interaction evidence.

To identify the genetic drivers of chromatin accessibility in different cell types, the researchers performed ATAC-QTL (aQTL) analysis at the major cell type level. They identified 9,628 genetically-associated peaks (gPeaks) across multiple cell types, with microglia showing strong enrichment for AD-GWAS signals. Of particular interest were 631 variants that exhibited shared genetic effects between AD-GWAS and aQTLs in microglia, including both genome-wide significant and sub-threshold loci. A total of 69 aQTL-GWAS colocalization events were identified, providing insights into potential regulatory mechanisms driving AD. For instance, rs77972827 near the SCIMP locus colocalized as both an aQTL in excitatory neurons and an eQTL in L2–3 excitatory neurons, underscoring the cell-type-specific regulatory role of this variant in AD.

The study also performed differential analysis to map AD-related transcriptomic and epigenomic changes. Significant changes in gene expression and ATAC peak accessibility were identified in microglia, with up-regulated microglial genes strongly enriched for AD risk loci. The researchers identified 15 differential regulatory modules between non-AD and early-AD, dominated by changes in excitatory neurons, and 74 differential modules between early-AD and late-AD, with glial differences predominating. Notably, microglia showed increased accessibility in regulatory modules associated with extracellular matrix remodeling and interleukin-11 signaling.

When investigating changes in cell type composition, the study found no significant neuronal loss in prefrontal cortex samples based on transcriptomic data, but the snATAC-seq data revealed a decrease in neurons, particularly excitatory neurons. Astrocytes, on the other hand, showed a decrease in composition in the snRNA-seq but not in the snATAC-seq data. Subtype analysis revealed a significant decrease in a specific inhibitory neuron subtype during AD progression, further highlighting the differences between the transcriptomic and epigenomic changes across AD stages.

These findings reinforce the critical role of microglia in AD, highlighting their involvement in both genetic regulation and the epigenomic landscape of the disease. The study provides new insights into the regulatory mechanisms and genetic variants that could be targeted for therapeutic strategies in AD. By integrating genetic, epigenetic, and transcriptomic data, the researchers have constructed a comprehensive map of AD-associated changes across different brain cell types.

The prioritization of Alzheimer's disease (AD) GWAS variants was carried out using epigenomic annotations and peak-to-gene links, revealing cell-type-specific overlaps across various loci. Nearly all the loci overlapped microglial peaks, consistent with previous findings of heritability enrichment in microglia. Additional overlaps were observed in astrocytes and excitatory neurons, with notable exceptions, such as three loci found exclusively in microglial peaks near genes like SPI1 and TREM2. Several loci were prioritized across multiple cell types, including BIN1, CLU, and APP. Functional prioritization of AD-GWAS variants identified eight genes specific to microglia, including PICALM, SCIMP, JAZF1, and HLA-DRB1, while other loci were found to be prioritized across cell types. Notably, 16 of the 19 prioritized microglial genes had previously been finemapped, and three potentially downstream targets, KANSL1-AS1, ACE, and CARF, were identified. These variants, particularly in microglia, were found to disrupt transcription factor binding sites like SPI1, suggesting disruption to microglial-specific regulatory circuitry. For instance, the rs9648346 variant in the JAZF1 locus, identified as a lead AD-GWAS variant, was shown to disrupt an SPI1 binding site and target the JAZF1 gene, a transcriptional repressor implicated in tau phosphorylation. Similarly, the PICALM locus was prioritized to regulate PICALM in microglia based on single-cell eQTL and interaction evidence.
In a more detailed exploration, ATAC-QTL (aQTL) analysis identified 9,628 genetically-associated peaks (gPeaks) across several major cell types, including microglia. The microglial epigenome was strongly enriched for AD-GWAS signals, with 631 variants shared as both aQTLs and AD risk loci. Although there was little overlap between aQTLs and AD-GWAS loci, 69 loci were identified where aQTLs co-localized with AD-GWAS, supporting their potential regulatory roles in AD etiology. For example, rs77972827 near the SCIMP locus exhibited aQTL effects in excitatory neurons and was also an eQTL for SCIMP in L2–3 excitatory neurons. However, most of the colocalized loci showed discordant or absent eQTL effects, emphasizing the complexity of these regulatory mechanisms. Furthermore, heritability enrichment analysis showed that AD-GWAS risk loci were not enriched for aQTL gPeaks in any cell type, suggesting that aQTLs and AD-GWAS loci represent distinct regulatory networks.

Gene expression and ATAC peak changes across major cell types were found to be consistent with the AD disease progression stages. In microglia, ATAC peaks linked to differential genes were enriched for AD risk loci, particularly for upregulated microglial genes. Differential ATAC

peak analysis revealed changes in co-accessibility modules during AD progression, with early AD showing changes dominated by excitatory neuron-related modules, while late AD exhibited glial differences, particularly in oligodendrocytes and oligodendrocyte precursor cells (OPCs). Microglia showed increased accessibility in regulatory modules associated with extracellular matrix remodeling and interleukin-11 signaling. Cell-type composition analysis in both snRNA-seq and snATAC-seq data indicated that while neuron loss in AD is common in regions like the hippocampus, no significant neuronal fraction changes were observed in the prefrontal cortex, suggesting an epigenome-specific loss of neuronal identity. Astrocyte composition decreased in the snRNA-seq data but not in snATAC-seq, indicating differential transcriptional and epigenomic changes. Specific subtypes within neurons and glial cells also displayed compositional changes, with a significant decrease in an inhibitory neuron subtype. These findings highlight the complex transcriptional and epigenomic landscape of AD, with distinct alterations observed across cell types and disease stages.

The integration of transcriptional and epigenomic data provides a deeper understanding of how gene regulation is altered across different cell types during Alzheimer's disease progression. By analyzing changes in chromatin accessibility and gene expression, this study uncovers distinct regulatory shifts that correspond to various disease stages, emphasizing the dynamic nature of epigenomic alterations in neurons and glial cells. The findings underscore the importance of linking non-coding regulatory elements to functional gene networks, offering insights into cell-type-specific vulnerability and adaptation in AD. Through this approach, researchers aim to refine genetic risk models and identify novel molecular targets, ultimately advancing the development of precision therapeutics for neurodegenerative diseases.

Discussion

This study presents a comprehensive analysis of the transcriptional and epigenomic landscapes of over 800,000 individual nuclei from postmortem prefrontal cortex samples of 92 individuals in the ROSMAP cohort, highlighting regulatory mechanisms underlying Alzheimer's disease (AD) progression. Utilizing an iterative computational framework, the researchers integrate single-nucleus ATAC-seq and RNA-seq data to construct peak-to-gene regulatory circuits, classifying cell-type-specific regulome dynamics. By establishing a direct connection between non-coding regulatory elements and their target genes, this study enhances the functional interpretation of AD-associated genetic variants, a crucial step toward refining genetic risk models and identifying molecular targets for therapeutic intervention.

Through this integrative approach, the study identifies ATAC-QTLs, prioritizes AD-GWAS variants, and maps their target genes, providing insights into the non-coding genome. The findings demonstrate that epigenomic alterations occur in a coordinated manner, affecting similar biological pathways within specific cell types and contributing to shifts in cellular composition. Despite the variation of single-cell measurements, the analytical framework presents non-coding enhancer activity, transcriptional regulation, and downstream pathway perturbations in AD. These insights could serve as a valuable reference for future research in neurodegenerative diseases, as the computational methodologies developed in this study may be applied to other disorders where gene regulation plays a critical role.

A key discovery is the occurrence of epigenomic erosion, characterized by widespread chromatin dysregulation in late-stage AD, where repressive regions become more accessible and open chromatin regions lose accessibility. This epigenomic instability corresponds with progressive loss of cellular identity, suggesting a continuation of regulatory disruption throughout disease progression. These findings raise critical questions regarding the causality of epigenomic erosion concerning transcriptional dysregulation and neurodegeneration. Understanding the mechanisms driving epigenomic erosion could provide new therapeutic avenues by targeting chromatin-modifying enzymes to restore normal regulatory function. Moreover, identifying key regulators involved in chromatin destabilization could reveal potential drug targets aimed at preserving cellular identity and preventing neuronal dysfunction. Overall, this dataset and analytical framework offer a high-resolution, cell-type-specific perspective on AD regulatory architecture, advancing the field's capacity to interpret genetic risk loci, clarify molecular mechanisms of disease progression, and identify novel therapeutic targets. By linking regulatory circuits across disease stages, this resource provides a foundation for mechanistic investigations into AD pathogenesis and broader applications to other neurodegenerative disorders. The ability to integrate both common and rare genetic variants within a unified regulatory framework not only enhances understanding of AD's genetic architecture but also establishes a precedent for studying complex neurodegenerative diseases through a systems biology approach. As a result, this work holds significant potential for informing precision medicine strategies, enabling the development of targeted interventions tailored to individual genetic and epigenomic profiles.

By establishing a high-resolution, cell-type-specific regulatory framework, this study paves the way for more precise interpretations of genetic risk loci and molecular mechanisms driving Alzheimer's disease progression. The ability to integrate regulatory circuits across different disease stages not only enhances our understanding of AD's genetic architecture but also sets a foundation for applying similar approaches to other neurodegenerative disorders. However, while chromatin accessibility data from ATAC-seq provides valuable insights, further refinement through complementary techniques is necessary to fully characterize the functional states of regulatory elements. Incorporating histone ChIP-seq could help differentiate active enhancers from poised or repressed elements, offering a more nuanced view of epigenomic regulation in AD. These advancements would strengthen our ability to link genetic variants to disease mechanisms and inform targeted therapeutic strategies tailored to individual genetic and epigenomic profiles.

Limitations

Building upon our current findings, several future directions and improvements can enhance our understanding of epigenomic dynamics in Alzheimer's disease (AD). While ATAC-seq provides a broad view of chromatin accessibility, it does not offer insight into specific chromatin states such as enhancers versus promoters or active versus poised elements. To achieve a more comprehensive characterization of the epigenomic landscape, integrating ATAC-seq with histone ChIP-seq would be instrumental. Histone modifications serve as key indicators of functional chromatin states, and their inclusion would refine the interpretation of chromatin accessibility changes, particularly in the context of AD progression. By leveraging histone ChIP-seq, it would be possible to distinguish between regulatory elements with distinct roles in

gene expression regulation, thereby providing a more detailed understanding of the epigenomic mechanisms underlying AD pathology.

Additionally, while this study incorporates computational approaches to align chromatin accessibility data from ATAC-seq with gene expression profiles obtained from RNA sequencing, a critical limitation remains in the asynchronous nature of these datasets. Because the transcriptomic response to epigenomic changes is often time-dependent, measuring chromatin accessibility and gene expression in separate nuclei may introduce discrepancies that obscure dynamic regulatory interactions. A concurrent multiomic approach that simultaneously profiles chromatin accessibility and gene expression within the same nucleus would significantly enhance the resolution of regulatory circuit maps. This would allow for a more precise characterization of the relationship between chromatin accessibility and transcriptional output, reducing uncertainties associated with computational alignment and better capturing disease-associated regulatory perturbations.

Another crucial area for future exploration is the temporal progression of epigenomic erosion in AD. While this study identifies epigenomic erosion as a hallmark of late-stage AD, a detailed trajectory of its emergence and progression remains unclear. Understanding the stepwise alterations in chromatin accessibility that precede widespread erosion would provide insights into the early molecular events that contribute to disease pathology. To construct a time-series framework of AD progression, future research must integrate multi-scale analyses across individuals, brain regions, and cell types. Investigating epigenomic changes within specific neural subpopulations and their spatial relationships to AD pathology will be critical in unraveling the mechanisms driving chromatin instability. Additionally, examining molecular alterations in cells before and after erosion may reveal key regulatory factors involved in maintaining chromatin integrity and highlight potential therapeutic targets for mitigating epigenomic degradation in AD. By adopting a multifaceted approach that incorporates spatial and temporal dimensions, a clearer picture of how epigenomic erosion unfolds during AD progression can be established, offering deeper mechanistic insights and potential avenues for intervention.
A deeper exploration of the temporal dynamics of epigenomic erosion could provide crucial insights into the early molecular changes that precede widespread chromatin instability in Alzheimer’s disease. While this study establishes epigenomic erosion as a hallmark of late-stage AD, tracing its emergence over time requires a multi-scale approach that incorporates analyses across individuals, brain regions, and cell types. Investigating these progressive changes in chromatin accessibility within specific neural subpopulations may help unravel the mechanisms that drive AD-related chromatin instability. By integrating these findings with transcriptomic and regulatory data, researchers can refine models of AD progression and identify key molecular factors involved in maintaining chromatin integrity. This approach not only deepens our understanding of disease mechanisms but also lays the groundwork for developing precision medicine strategies that target early epigenomic disruptions before irreversible neuronal damage occurs.

Conclusion

This comprehensive study advances our understanding of Alzheimer's disease (AD) by integrating epigenomic and transcriptomic analyses at the single-cell level. By examining over

850,000 nuclei from the prefrontal cortexes of 92 individuals, the research delineates the brain's regulome, encompassing chromatin accessibility landscapes, transcriptional regulators, co-accessibility modules, and peak-to-gene associations in a cell-type-specific manner. The findings highlight that AD risk loci are predominantly enriched in microglial enhancers and associated with transcription factors such as SPI1, ELF2, and RUNX1. Notably, the study identifies 9,628 cell-type-specific ATAC-QTL loci, facilitating the prioritization of AD variant regulatory circuits. Moreover, differential accessibility of regulatory modules is observed, with glial cells affected in late-stage AD and neurons in early-stage AD. A striking discovery is the global epigenome dysregulation in late-stage AD brains, indicative of epigenome erosion and loss of cell identity. Collectively, these insights enhance our understanding of AD's pathogenesis and may inform the development of targeted therapeutic strategies.

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