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Modeling Alzheimer's disease with human multi-omics profiles: Promise to personalized medicine

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Alzheimer's disease (AD) presents considerable heterogeneity in disease risk and outcomes, posing a major challenge for effective therapeutic development. Recent advances in multi-omics profiling are revolutionizing our understanding of the complex AD pathogenesis. Leveraging long-read sequencing and large-scale multi-ancestry genetic studies, researchers are unraveling the complex polygenic architecture of AD. Additionally, advances in multi-omics techniques unlock the power of molecular profiling of human biological samples, particularly spatial omics of human postmortem brain tissues and molecular profiling of biofluids, to understand the complex AD pathogenesis. Importantly, artificial intelligence (AI)-driven approaches integrate multimodal data to identify molecular features associated with disease risk and endophenotypes, fostering sophisticated models for disease risk predictions and molecular-based patient stratification. Coupled with human-induced pluripotent stem cell-derived brain cell models for validation and mechanistic studies, this comprehensive AI-integrated, multi-omics study approach promises to delineate both shared AD pathological processes and individual variations, paving the way for personalized medicine.

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by significant heterogeneity in disease risk, progression, and outcomes among patients. This variability stems, in part, from the polygenic nature of AD, with over 80 identified genetic risk loci [1–3]. Tools that capture these variations are critical for understanding the diverse biological processes underpinning the complex disease pathogenesis. Recent advances in multi-omics profiling with human tissues and biofluid samples enhance our understanding of patient heterogeneity and the diverse molecular mechanisms leading to the disease. This review highlights recent advances in multi-omics studies and their integration with machine learning (ML)-driven models to drive therapeutic development and pave the way for personalized medicine.

Understanding and predicting disease risk with large-scale genetic studies

The identification of AD-associated single-nucleotide polymorphisms (SNPs) through large-scale SNP-array and whole-genome sequencing studies has provided critical insights into AD pathogenesis beyond neuronal dysfunction. Notably, common AD risk variants enriched in innate immune processes and rare *TREM2* variants have highlighted the role of microglia in AD pathogenesis [3,4]. Yet, the currently identified genetic risk factors do not fully explain the observed heritability of AD, suggesting that some genomic complexities remain unexplored. For instance, structural variants (SVs), affecting over 50 base pairs of genomic region, have shown a strong association with AD risk but are largely understudied [5–7]. Advances in long-read sequencing (LRS) provide precise information on the sequence and breakpoint of SVs, enabling sensitive discoveries and genotyping of SVs using large-scale short-read sequencing data [8,9]. The discovery of genetic factors associated with AD has led to the development of polygenic risk score (PRS) models, which can predict AD risk and related endophenotypes [10,11]. Future enhancements will come from incorporating large-scale multi-ancestry genetic data cohorts as some genetic loci (e.g., *APOE*) show ethnic variability [12,13]. Expanding multi-ancestry genetic data cohorts in conjunction with LRS will enhance the precision of future PRS models for disease risk prediction and patient stratification for both research and clinical applications.

Decoding complex AD pathogenesis with human multi-omics profiling

Multi-omics analyses of human biological samples reveal AD-associated molecular alterations, providing critical insights into disease pathogenesis. Human postmortem brain tissue provides the most direct evidence on AD-related molecular alterations, and recent advances enable single-cell resolution studies with spatial context. While these data capture terminal molecular and pathological outcomes, they are limited in reflecting dynamic changes across disease progression. Conversely, fluid biomarkers in cerebrospinal fluid (CSF) and blood offer a platform for timely and systemic assessment of disease status, enabling longitudinal monitoring and therapeutic evaluation. Integrating multi-omics data with ML-driven models holds promise for deepening our understanding of AD pathogenesis and accelerating the identification of novel therapeutic targets.

(1) Cell-type and regional-specific responses in the human postmortem brain

Single-cell level molecular profiling studies have revealed the heterogeneity within cell types. Recent advances in spatial omics provide critical information on the distribution of cellular subpopulations across brain regions and their interactions with neighboring cells and the microenvironment. Studies have identified molecular signatures associated with excitatory and inhibitory neuronal subpopulations in vulnerable regions that are altered in AD, shedding light on the mechanisms underlying neuronal vulnerability and protection [14—17]. Specifically, alterations in Reelin signaling, impaired protein folding functions, and increased apoptotic processes have been implicated in the selective vulnerability of excitatory and inhibitory neuronal populations [15,17]. Aside from neurons, microglia exhibit diverse molecular subtypes, highlighting their dynamic responses to environmental cues [18—20]. Spatial-omics studies revealed that microglia displayed a continuum of changes in their proteomic signatures associated with immune activation across brain regions. In AD brains, microglia exhibit a high continuum of activated phenotypes characterized by elevated CD33 and CD44, which are found in close proximity to inhibitory neuronal and reactive astrocytic proteins [21]. Moreover, studies provide insights into molecular interactions underlying neuron-microglia communications in the AD brain. For instance, studies identified diminished molecular interactions between microglia and nearby stress neurons (i.e., APP-CD74 ligand receptor pair) that promote Aβ clearance in the AD brain and the FGF2-FGFR3 signaling mediating beneficial neuron-microglia communication that supports neuronal health after Aβ immunization [16,22]. Collectively, these studies enhance our understanding of complex AD pathogenesis at cell-type and region-specific levels, which provide critical insights into promising therapeutic candidates that drive specific cellular responses against AD brain pathology with spatial specificity.

(2) Systemic evaluation of individuals' disease status with human cerebrospinal fluid (CSF) and blood

Fluid biomarkers in CSF and blood provide quantitative indicators of AD-related pathological changes across disease progression, categorized by the "A (Aβ)/T (tau)/N (neurodegeneration)" framework [23,24]. Notably, the blood protein biomarker pTau-217/Aβ42 ratio is now Food and Drug Administrationapproved to assist in AD diagnosis [25]. Beyond these core categories, large-scale proteomic studies of AD biofluids reveal that while CSF primarily reflects brain-derived and central nervous system (CNS)-adjacent processes, blood integrates CNS-linked signals with contributions from peripheral organs and circulating immune cells. These studies consistently show dysregulation in biological processes beyond the A/T/N framework [26—29], including immune-related processes (e.g., inflammatory signaling, complement activation), vascular pathways (e.g., BBB-related dysfunction, angiogenic and coagulation signaling), and metabolic activities (e.g., lipid transport, mitochondrial stress) [30—33]. These multipathway changes support a comprehensive, systems-level view of AD pathogenesis, highlighting disease-relevant mechanisms operating across the brain—periphery axis [28,31,33,34]. Importantly, several of these alterations, particularly immune and inflammatory signatures in blood, are observed early in the AD continuum, suggesting roles in disease initiation or propagation and underscoring their value for early detection [31]. Blood cell transcriptomic analyses also reveal that the expression of gene modules related to myeloid leukocyte activation decreases during AD progression, further indicating the involvement of peripheral leukocytes in the disease [35].

In addition to providing insights into molecular alterations underlying the diverse biological processes leading to AD, capturing multipathway changes enables patient stratification based on molecular profiles for personalized disease management. Recent studies demonstrate the use of CSF proteomic profiles for stratifying individuals into subtypes associated with specific pathological processes and clinical outcomes [32,36]. For instance, a subtype characterized by molecular alterations related to neuronal hyperplasticity is associated with longer survival, illustrating how molecular profiles can connect specific biological process

dysregulation with clinical outcomes [32]. Altogether, biofluid molecular profiles offer a valuable platform for studying diverse biological processes contributing to AD manifestation and progression, forming the basis for developing molecular-based patient stratification models to identify suitable populations for clinical trials.

(3) Leveraging multi-omics data to model AD trajectory and discover therapeutic targets

Advances in artificial intelligence (AI) are unlocking the potential of increasingly complex and large-scale human multi-omics data. Machine learning (ML) models, in particular, excel at making predictions from high-dimensional datasets by identifying important features and mapping intricate relationships [37,38]. Recent studies leverage AI to decode AD multi-omics profiles, enhancing precision in disease risk modeling and accelerating therapeutic target discovery [37–41]. For instance, integration of ML algorithms with CSF and blood proteomes can model AD-related endophenotypes, including accelerated brain aging, amyloid and tau pathology, and cognitive resilience [34,42,43]. These models achieve accurate early predictions of long-term AD risk and cognitive decline, forecasting outcomes up to 10–17 years in advance, thus paving the way for early intervention. In addition to risk predictions, these approaches facilitate the establishment of biological causality. Researchers are combining genetic causal inference methods, such as Mendelian randomization and colocalization analyses, with ML approaches. For instance, after ML identified vascular and immune-related plasma protein candidates that predict brain atrophy in AD, the subsequent discovery of genetic variants linked to brain structure that influence levels of candidate protein provides crucial evidence for a causal relationship between these molecular candidates and brain structure [44]. This integration of study approaches is critical for elucidating potential molecular drivers of neurodegeneration in AD as well as for accelerating AI-driven therapeutic target discovery and drug repurposing. For example, network-based multi-omics platforms employing graph representation learning enable the prioritization of novel biomarkers and *in silico* drug repositioning candidates [40]. Interrogating multi-omics data through combined ML and genetic causal inference provides a powerful, data-driven strategy to forecast AD progression and uncover its underlying mechanisms.

Future direction: The road to personalized disease management strategies

Delineating the heterogeneity in AD is a major hurdle for personalized disease management. Genetic studies and molecular profile analyses have already revealed variations at the genomic and molecular levels. Recent AI-driven approaches, leveraging the integration of multimodal data, are instrumental in predicting disease risk, stratifying patients, and deciphering the regulatory roles of genetic variants, providing the foundation for uncovering novel pathophysiological pathways. These models facilitate rapid hypothesis generation, improving understanding of the impact of genetic risk factors and enhancing clinical trial efficiency and success [45–47]. Foreseeing the future, increased multimodal data types (e.g., genomic, molecular profile of human biological tissues, neuroimaging, clinical data), higher data resolution (e.g., long-read sequencing), and larger multi-ancestry datasets will improve model performance for robust disease prediction and patient stratification. Advances in human induced pluripotent stem cell (iPSC)-derived brain cell models, including microfluidic-based blood–brain barrier models and assembloids, offer genetically relevant platforms with physiological relevance for validating model findings and for drug screening [48–50]. From AI-driven disease modeling to patient-derived iPSC models, decoding heterogeneity will enable personalized disease management and identify common pathophysiological pathways for therapeutic development.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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