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REVIEW ARTICLE

Leveraging multiomic approaches to elucidate mechanisms of heterogeneity in Alzheimer's disease: Neuropsychiatric symptoms, co-pathologies, and sex differences

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Abstract

The heterogeneity of Alzheimer's disease (AD) is multi-dimensional, encompassing clinical features such as neuropsychiatric symptoms (NPS), rate of progression, age of onset, comorbidities, and neuropathological features such as co-pathologies, and represents the diverse outcomes of manifold genetic and environmental risk

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determinants. These diverse features of AD also vary significantly between sexes and across ancestral backgrounds, but the specific variations and causal mechanisms are not well understood. Recent technological advances, particularly single-cell and spatial omics, have provided new tools to dissect the molecular underpinnings of AD heterogeneity and its multifactorial nature. This perspective review highlights molecular differences, general and sex-specific, that contribute to the heterogeneity of AD in aspects such as NPS, co-pathology prevalence, and general disease trajectories. We further examined the potential for multiomic approaches to direct future translational studies aimed at the development of precision medicine strategies for the treatment of AD in all its diverse forms.

KEYWORDS
Alzheimer's disease, co-pathologies, disease heterogeneity, disease subtypes, epigenomics, genetic diversity, multiomics, neuropsychiatric symptoms, proteomics, quantitative trait locus mapping, sex differences, single-cell sequencing, spatial omics, transcriptomics, translational science

Highlights

- Alzheimer's disease (AD) represents diverse subtypes characterized by comorbid clinical symptoms and co-pathologies.
- Integration of bulk, single-cell, spatial multiomics reveals factors underlying AD variation.
- Multiomics studies indicate shared and distinct mechanisms between major psychiatric disorders and AD.
- Multiomics data have transformative implications for sex- and population-specific AD therapies.
- New tailored precision medicine strategies are needed to address the full range of complexity in AD.

1 | INTRODUCTION

Alzheimer's disease (AD) is a highly heterogeneous age-related neurodegenerative disorder with divergent clinical and pathologic characteristics from case to case and across demographics, as well as frequent comorbidity with other neuropathologies and clinical presentations (Figure 1, upper panel). Thus, AD should be considered a multifaceted rather than a monolithic disorder, with numerous factors driving disease manifestation. This multifactorial nature of AD presents a challenge in capturing the genetic complexity and molecular subtypes underlying the diversity in AD characteristics. Over the years, functional genomics studies and integrated multiomics datasets have provided important mechanistic insights into AD genetics, including the identification of candidate genes within associated risk loci, and established the role of gene dysregulation in AD pathogenesis. Specifically, these studies examined specific disease-related genes,[1,2] pathways,[3] differential transcriptome profiles,[4] DNA methylation,[5–8] histone modification landscapes,[9] expression quantitative trait loci (eQTLs),[10–12] and other omics QTLs in human brain tissues (Figure 1, middle panel). However, until recent years, most brain functional genomics studies have generated omics datasets using bulk brain tissue homogenates that amalgamate various types of neurons and glial cells. While these studies have produced important data, the heterogeneity of bulk brain tissue makes it difficult to determine the specific cell types and subtypes responsible for changes in gene expression and the chromatin landscape. Bulk analysis can also mask signals corresponding to a particular cell subtype, especially if the causal cell subtypes comprise a small fraction of the entire sample. An additional shortcoming of bulk brain tissues is the bias associated with sample-to-sample variation in the cellular composition of the tissue. Variability in cell subtype proportions across samples is even more pronounced when analyzing disease-affected brain tissues impacted by neurodegenerative processes such as neuronal loss and gliosis. The recent development of single-cell experimental approaches has provided a means of circumventing many of the limitations of bulk tissue analysis. Over the past ≈ 5 years, the AD functional genomic field has transitioned into single-cell multiomics research, enabling the identification of epigenomic and transcriptomic changes associated with AD with a previously

unattainable cell-subtype level of precision.[13,14] Spatial omics studies have added another dimension to the understanding of AD pathology by allowing the comparison of gene expression and epigenetic features across specific brain regions within the same experimental subjects.

Despite these advances, a persistent major gap in AD omics research stems from the fact that most studies have applied a case–control design in examining AD-associated differences without taking into account the heterogeneous nature of the disease. This heterogeneity is multi-dimensional, encompassing clinical features such as neuropsychiatric symptoms (NPS), rate of progression, age of onset, comorbidities, and neuropathological features such as co-pathologies, among other factors, and represents the diverse outcomes of manifold genetic and environmental risk determinants. These diverse features of AD also vary significantly between sexes and across ancestral backgrounds, but the specific variations and causal mechanisms are not well understood. With that said, recent technological advances, particularly single-cell sequencing and spatial transcriptomics, provide new tools to dissect the molecular underpinnings of AD heterogeneity and its multifactorial nature.

Here, we provide an expert perspective on how multiomic approaches—integrating data from genomics, transcriptomics, epigenomics, proteomics, and metabolomics—can provide insights into the (1) clinical, (2) neuropathological, and (3) demographic heterogeneity and associated differential risk factors observed in AD. With regard to clinical heterogeneity, we focused on studies examining clinical phenotypes relating to the comorbidity of NPS with AD, including apathy, agitation, depression, and psychosis, as these are among the most prominent AD comorbidities and omics methods have been applied extensively to this area of AD research. We discuss the potential for multiomic data to identify unique molecular signatures and potential mechanisms driving these symptoms. These profiles will define AD molecular subtypes that differ in clinical characteristics, offering opportunities for precision medicine. With this in mind, we discuss our perspective on translating the disease molecular subtypes into more effective and accurate treatments of NPS in AD, conceptualized around personalized medicine. Regarding the neuropathological aspect, we discuss the intersection of AD with co-pathologies, including Lewy body (LB) pathology, transactive response DNA binding protein 43 kDa (TDP-43), and vascular lesions, which frequently coexist with AD pathology and may have a vital impact on AD pathogenesis. By integrating multiomic data, researchers have worked to better understand how these co-pathologies contribute to clinical variability in AD. The molecular phenotypes associated with these various co-pathologies are informative toward the understanding of disease trajectory and AD molecular subtypes that differ in their neuropathological characteristics. Finally, we address the effect of population diversity in AD, with a focus on differences in disease manifestation and risk between male and female populations, as sex has been established as one of the most important demographic factors influencing AD incidence and outcome, and the relationship between sex and AD has been extensively studied via omics approaches in recent years. We describe studies probing the impact of sex on disease risk, progression, and response to treatment. Overall, this perspective review highlights molecular differences, general and sex-specific, that contribute to the heterogeneity of AD in terms of NPS, co-pathology prevalence, and general disease trajectories, and examines the potential for multiomics approaches to direct future translational studies aimed at the development of precision medicine strategies for the treatment of AD in all its diverse forms.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors extensively reviewed the literature using traditional sources (e.g., PubMed). Recent technological advances, particularly single-cell sequencing and spatial omics methods, provide new tools to dissect the molecular underpinnings of Alzheimer's disease (AD) heterogeneity and its multifactorial nature. The authors investigated the application of these advancements to unravelling the various aspects of AD heterogeneity.
2. **Interpretation**: The synthesis of recent multiomics literature paints a picture of AD as a group of subtypes rather than a monolithic disorder, with subtypes characterized by differences in clinical features such as neuropsychiatric symptoms, rate of progression, age of onset, comorbidities, and neuropathological features such as co-pathologies, which vary significantly between sexes and across ancestral backgrounds.
3. **Future directions**: The work reviewed here has translational implications in multiple ways toward precision medicine in AD, including the development of genetic and molecular biomarkers, the discovery of specific therapeutic targets, and the design and implementation of clinical trials, with consideration of individual patient profiles.

2 | NEUROPSYCHIATRIC SYMPTOMS IN AD

2.1 | Heterogeneity of AD NPS

NPS refers to behavioral, psychological/psychiatric, and personality changes associated with neurodegenerative diseases. While primarily studied in the context of dementia, these changes are also known to occur in parallel with—and sometimes before—cognitive decline in preclinical AD and related dementias (ADRD).[15] In the context of dementia, the term behavioral and psychological symptoms of dementia (BPSD) is often used, while in preclinical/prodromal disease, the term mild behavioral impairment has been coined. Here, we use NPS to describe the full spectrum of symptoms linked to neurodegeneration. Most patients with late-onset AD (LOAD) have comorbid NPS, with apathy, depression, and anxiety being most prevalent.[16–23] Other common and clinically important NPS include agitation and psychosis. NPS

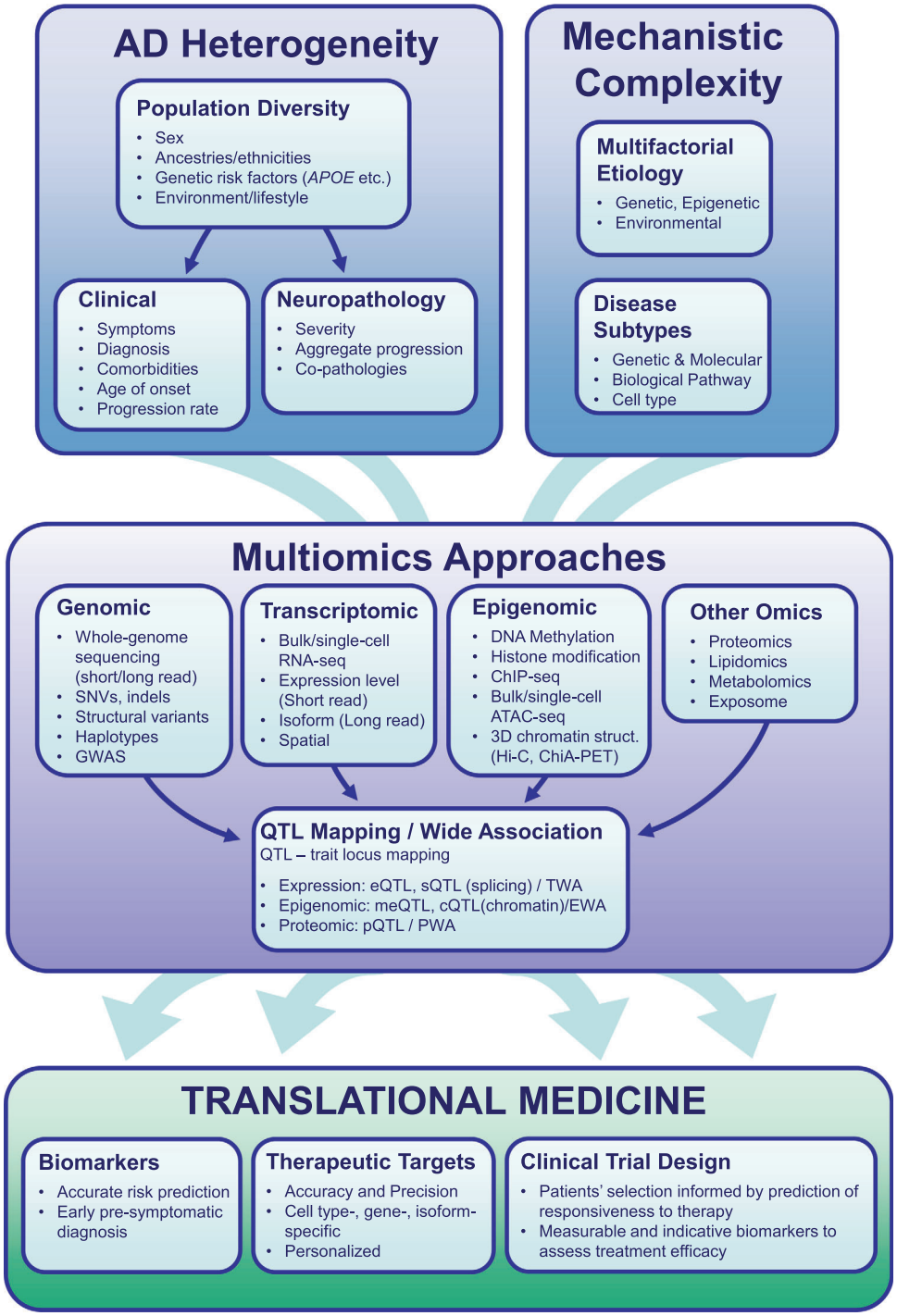

FIGURE 1 Omics approaches to unravel AD complexity and develop novel precision medicine strategies. AD is a highly complex disease, exhibiting heterogeneity with regard to symptom presentation (including neuropsychiatric symptoms), the presence of co-pathologies in many AD cases, sex differences, and many other factors including diversity of ancestral background. Omics methods can help unravel this complexity and provide a basis for translational research into the development of biomarkers for risk assessment and early detection, identification of new cell type–specific molecular targets for therapeutics, and novel precision medicine strategies taking into account the many complexities shaping AD pathogenesis in individual cases. AD, Alzheimer's disease; *APOE*, apolipoprotein E; ATACseq, assay for transposase-accessible chromatin with sequencing; ChiA-PET, chromatin interaction analysis by paired-end tag; ChIPseq, chromatin immunoprecipitation sequencing; eQTL, expression quantitative trait loci; EWA, epigenome-wide association; GWAS, genome-wide association study; meQTL, methylation quantitative trait loci; pQTL, protein quantitative trait loci; PWA, proteome-wide association; QTL, quantitative trait loci; SNV, single nucleotide variant; TWA, transcriptome-wide association.

significantly impact patient quality of life, are associated with increased functional and cognitive decline, and increase caregiver burden and admission to care facilities.[24–26] When occurring in the prodromal phase, NPS also correlate with various physiological and pathological markers.[27,28] NPS typically accompany progressive cognitive decline, serving as both diagnostic and prognostic indicators of ADRD.

NPS domains have been identified using diverse methods, such as factor analysis, cluster analysis, and latent class analysis, often leveraging data from the National Alzheimer's Coordinating Center (NACC) to gain deeper insights into their comorbid patterns. For example, network analysis has identified five symptom clusters, with the largest group comprising agitation, disinhibition, irritability, and elation or euphoria.[29] A latent class analysis study[30] identified four distinct classes based on combinations of irritability, depression, apathy, nighttime behaviors, or lack of symptoms. Another study identified four components: behavioral dysregulation, psychosis, mood disorders, and agitation.[31] Each of these domains was associated with a younger age at AD diagnosis. Interestingly, none of the components were linked to the age at assessment, years of education, or apolipoprotein E (APOE) $\varepsilon 4$ carrier status.[31] While most studies have tended to group apathy and depression together, it is important to note that there is evidence that these are distinct syndromes. This is backed up by a data-driven examination identifying latent classes describing distinct apathy and depression groups.[32] Collectively, these studies highlight the potentially complex interactions among NPS, and except in the case of psychosis, there are few established guidelines on phenotyping for molecular studies.[33] This is an important gap that could impact the reproducibility and exploitation of drug targets. A key area of complexity is the relationship between neuropsychiatric disorders as risk factors and NPS as prodromal features of neurodegenerative disease. Specifically, there are three profiles to resolve, each of which may result from differing underlying mechanisms: (1) psychiatric symptoms as a predisposing risk factor occurring before the onset of AD pathology, (2) NPS as an early sign of neurodegenerative changes or a prodrome with or without cognitive deficits, (3) NPS occurring *de novo* in dementia.

Depression, apathy, and psychosis are among the most well studied across each of these profiles and multiomic studies, while in their nascent phase, have a clear role to play in elucidating underlying mechanisms. Major psychiatric disorders, such as major depressive disorder (MDD) and schizophrenia, increase the risk of dementia. For the typical early-mid-life onset, these are unlikely to represent prodromal neurodegenerative NPS; however, the increased dementia risk profile raises the possibility of shared etiologies and intersecting biological pathways with AD. However, depression, apathy, schizophrenia-like psychoses, and milder delusional ideation can emerge in later life, when they are associated with incident cognitive decline and biomarkers of AD.[27,34–37] In these cases, given the proximity to the onset of clinical dementia, it may be expected that a higher proportion of cases are prodromal, suggesting an important role for blood biomarkers in the clinical differentiation of symptoms due to neurodegenerative disease and primary psychiatric conditions. Finally, it is important to note that a history of psychiatric illness is not necessary to explain the presence of NPS in the context of established dementia. Indeed, clinical evidence of differing treatment responses to antipsychotics and antidepressants would suggest the existence of at least some distinct mechanisms.[38,39]

2.2 | Mechanistic research on NPS heterogeneity in AD

The pathogenesis of both AD and NPS is complex and involves polygenic risk and environmental factors. The genetic architecture underpinning the onset and heterogeneity of NPS in AD has been understudied, most likely due to a lack of appropriately phenotyped samples (ascertaining NPS status requires specialist *ante mortem* assessments, which are not universally available in biobank collections). However, recent years have seen an increase in studies (Table 1), which may be in part due to an increasing availability of cases and a specific funding call from the National Institutes of Health in 2018/2019.

Two notable milestones were the first genome-wide significant loci for psychosis in AD dementia (*SUMF1* and *ENPP6*) reported in a cohort of 12,317 cases[40] and the first differentially methylated regions of the genome (in *TBX15* and *WT1*).[41] Moreover, a bulk transcriptomic study identified a 98-gene signature associated with both the agitation and psychosis domains of NPS, while differential expression of 88 genes was linked to the affective, agitation, and psychosis domains, and a 28-gene module was linked to apathy, agitation, and psychosis.[42] However, no transcriptional signatures were associated with all four domains: affective, psychosis, agitation, and apathy. All these loci require replication and functional characterization. However, collectively these studies provide converging evidence of a distinct genetic basis for psychosis in AD that differentiates it from AD cases without psychosis (the molecular basis of other NPS is less clear from the research described). This is supported by SNP-based heritability estimates of 0.18 and 0.31 (depending on the method used).[40] Confirmation of this genetic basis has provided the essential foundations on which to build additional layers of omics data.

To that end, using weighted gene co-expression network analysis (WGCNA), a recent DNA co-methylation network study of psychosis in AD identified a module of co-methylated loci in the dorsolateral prefrontal cortex that replicated in an independent sample and was enriched in synaptic genes and inhibitory neurons.[43] Furthermore, integrating single-nucleotide polymorphism (SNP) data and genome-wide association study (GWAS) data from schizophrenia showed that methylation QTLs (mQTL) in the module co-localized with loci linked to schizophrenia. This suggestion of transdiagnostic mechanisms underpinning psychiatric symptoms across the lifespan from multi-level data is supported by prior studies linking AD psychosis to schizophrenia via analysis of polygenic scores,[44] and to depression and bipolar via genetic correlations.[40]

A more established field of research is the link between AD per se and major psychiatric conditions, which is driven by epidemiological observations of increased risk in people with lifelong mental health conditions like MDD. A genetic causal relationship has been observed between MDD and LOAD,[45] though other studies suggest there is no causal link.[46] Other prior work has elucidated the shared genetic

TABLE 1 Summaries of key studies using omics methods to examine the relationship between NPS and AD.

Study	Omics methods	Overall approach	Major findings
DeMichele-Sweet, M.A.A. et al. (2021)[40]	GWAS	Genome-wide association analysis of genetic loci in 12,317 AD subjects and 5445 AD + psychosis subjects.	*SUMF1* and *ENPP6* loci correlated significantly with psychosis in AD.
Pishva, E. et al. (2020)[41]	Methylomics	Analyzed methylomic variation in prefrontal cortex, entorhinal cortex, and superior temporal gyrus in 18 AD, 29 AD + psychosis donors.	Identified psychosis-associated methylomic changes in *AS3MT*, *TBX15*, and *WT1*.
Fisher, D.W. et al. (2024)[42]	Bulk transcriptomics	Transcriptome-wide analysis for affective, apathy, agitation, and psychosis domains of behavioral and psychological symptoms of dementia in AD using bulk RNA-seq of *post mortem* anterior cingulate cortex tissues.	98-gene signature associated with agitation and psychosis domains, 88-gene module linked to the affective, agitation, and psychosis domains, and a 28-gene module linked to apathy, agitation, and psychosis. Twenty-two DEGs associated with all domains, including *TIMP1*. Agitation DEGs enriched for extracellular matrix and post-synaptic genes. *ESR1* and *PARK2* were high-impact agitation-associated genes.
Kouhsar, M. et al. (2025)[43]	Methylomics, GWAS, mQTL mapping	Assessed brain DNA methylation in AD donors with and without psychosis, using the EPIC methylation array. Weighted gene correlation network analysis used to identify modules of co-methylated genes. Integrated with mQTLs and GWAS data.	Identified one AD + psychosis associated module, enriched for synaptic pathways in neurons. mQTLs the module co-localized with schizophrenia-linked loci.
Wingo, T.S. et al. (2022)[57]	GWAS, bulk transcriptomics, single-cell transcriptomics, proteomics	Integration of GWAS, bulk transcriptomic, proteomic, and single-cell data to examine shared mechanisms across major psychiatric and neurodegenerative diseases, including MDD and AD. Sex-stratified analysis.	Major psychiatric and neurodegenerative diseases have shared genetic susceptibility and pathophysiology. Identified 13 shared causal proteins, 118 interacting causal proteins, and the central role of synaptic transmission (involving the SNARE complex and SNAP receptor), immune function, and mitochondrial processes in the shared pathogenesis.
Lutz, M.W. et al. (2020)[60]	GWAS	Genetic pleiotropy analysis using LOAD and PTSD GWAS datasets from European and African ancestry populations, followed by functional-genomic analyses.	Identified strong enrichment for LOAD across the PTSD GWAS association and modest enrichment for PTSD in LOAD GWAS association.
Lutz, M.W. et al. (2020)[45]	GWAS	Pleiotropy analyses using LOAD and MDD GWAS data sets from the International Genomics of Alzheimer's Project and the Psychiatric Genomics Consortium.	Moderate enrichment for LOAD-associated SNPs with MDD GWAS. Numerous SNPs corresponded to 40 genes, including 9 known LOAD-risk loci in *SPI1* and *MS4A* gene regions, and novel risk loci for LOAD conditional with MDD.
Monereo-Sanchez, J. et al. (2021)[48]	GWAS	Applied Gaussian mixture modeling and conjunctional FDR analysis to GWAS summary statistics of AD and depression to identify overlapping loci. Effects of identified overlapping loci on AD and depression were tested in UK Biobank subjects and mapped onto brain morphology with MRI data.	Identified 98 overlapping causal genetic variants between AD and depression with mixed directional effects. An SNP in the *TMEM106B* gene was significantly associated with both disorders.
Gilchrist, L. et al. (2025)[46]	GWAS	Correlation of GWAS of depression symptoms from UK Biobank, GLAD study and PROTECT, with six AD GWAS.	Identified 20 significant genetic correlations of AD with depression symptoms, in 14 genomic regions. *TMEM106B* region showed colocalization between multiple depression symptoms and both clinical and proxy AD.
Gibson, J. et al. (2017)[47]	GWAS	Used population genotype data from Generation Scotland Scottish Family Health Study and UK Biobank to test whether MDD and AD have an overlapping polygenic architecture.	No evidence of a common polygenic structure for AD and MDD was identified, suggesting that these disorders are not determined by common genetic variants.
Hofstra, B.M. et al. (2024)[49]	GWAS, eQTL mapping	Used depression and AD GWAS catalog SNPs, brain-specific eQTL data, and a hippocampal gene co-expression network to examine shared genetics of AD and depression.	Did not identify direct genetic overlap between AD and depression but found six shared eQTL genes: *SRA1*, *MICA*, *PCDHA7*, *PCDHA8*, *PCDHA10*, and *PCDHA13*, and convergent pathways relating to synaptoimmunology and trans-synaptic signaling.

Abbreviations: AD, Alzheimer's disease; DEG, differentially expressed gene; eQTL, expression quantitative trait loci; FDR, false discovery rate; GWAS, genome-wide association study; LOAD, late-onset Alzheimer's disease; MDD, major depressive disorder; mQTL, methylation quantitative trait loci; MRI, magnetic resonance imaging; NPS, neuropsychiatric symptoms; PTSD, post-traumatic stress disorder; SNP, single nucleotide polymorphism.

architecture between AD and either MDD or depressive symptoms,[45,47–49] identifying common genetic pathways, such as immune system, synaptic signaling and organization, myelination, development, and inflammatory pathways.[45,49] Alteration of gene expression and mechanisms dysregulating gene expression have been suggested to play a prominent role in the genetics underlying AD pathogenesis. Differential gene expression has been widely reported in AD,[14,50,51] with studies uncovering differentially expressed genes (DEG) in bulk brain tissues[51] and within different brain cell types[14] cross-sectionally and throughout disease progression. Single-nucleus RNA sequencing (snRNA-seq) studies have enabled the investigation of the cellular heterogeneity of gene expression at the cellular subtype level for specific regions of the brain. snRNA-seq studies have reported on cellular subtype–specific gene expression changes in AD[13,52,53] and in depression or MDD,[54–56] presenting results at the gene and biological pathway level.

Integration of multiple data types (GWAS, transcriptomic, single-cell) was performed in a comprehensive study of the shared mechanisms across major psychiatric and neurodegenerative diseases, including MDD and AD.[57] The results of this study reported that synaptic transmission, particularly involving the SNARE complex and SNAP receptor, constitutes part of the shared mechanisms among these psychiatric and neurodegenerative diseases.[57] The study showed that major psychiatric and neurodegenerative diseases have shared genetic susceptibility and pathophysiology and identified 13 shared causal proteins; 118 interacting causal proteins; and a central role for synaptic transmission, immune function, and mitochondrial processes in the shared pathogenesis.[57] Of note, this study showed results that were consistent with a model of AD in which mitochondrial dysfunction occurs early in the progression to neurodegeneration and continues into the late stages of the disease. Shared mitochondrial mechanisms are more likely to act early in the disease process, as psychiatric disorders typically have an onset age in early adulthood or midlife, whereas neurodegenerative diseases emerge later in life.[57] This aligns with prior research,[58,59] as well as two additional studies investigating shared genetic etiologies between AD and post-traumatic stress disorder (PTSD)[60] and between AD and MDD.[45] Collectively, these studies indicate the existence of shared mechanisms between major psychiatric disorders and AD.

2.3 | Omics datasets available to study NPS heterogeneity in AD

Studies of the heterogeneity of NPS in AD have used various sources of omics data, including the AD Knowledge Portal,[61] project and consortium data including Psych-AD and Psych-ENCODE, and large-scale data resources available to the research community, for example the UK Biobank and the NACC. These datasets comprise a wide variety of types of omics data (genetic, transcriptomic, proteomic) and specific NPS. Table 2 lists several of the datasets available for research with illustrative studies and publications.[29,43,54,57,62–76] New data are made available frequently; as an example, the snRNA-seq data in the Psych-AD project were recently made available, along with data for NPS. These datasets cover a spectrum of NPS in addition to clinical conditions or symptoms, including MDD and bipolar disease. While the focus of this review article is on NPS in AD, some of these resources contain data on other neurodegenerative diseases including Parkinson's disease (PD), dementia with LB (DLB), and frontotemporal dementia (FTD). Future studies investigating the mechanisms underlying NPS may leverage large-scale efforts like brainSCOPE, GTEx, and UKB-PPP, to better understand how genetic variants influence cell-level[74] and bulk gene expression,[71,77,78] and proteome expression.[67]

3 | CO-PATHOLOGIES IN AD

3.1 | Prevalence, distribution, and clinical implications of AD co-pathologies

More than 50% of individuals diagnosed with AD are found at *post mortem* to exhibit additional neuropathological features beyond the classical hallmarks of extracellular amyloid beta (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau (PMID: 39379761). These co-pathologies often include protein aggregate-based abnormalities characteristic of other neurodegenerative diseases. Among the most frequently observed are LB pathology, consisting of neuronal aggregates of hyperphosphorylated and misfolded alpha-synuclein, and TDP-43 proteinopathy, marked by the cytoplasmic mislocalization and aggregation of the RNA-binding protein TDP-43. Cerebrovascular lesions (macrovascular large-vessel atherosclerosis, small-vessel/arteriolosclerosis, cerebral amyloid angiopathy), hippocampal sclerosis, and argyrophilic grain disease are also commonly seen, further contributing to the complexity of the disease landscape. As such, the boundaries between neuropathological disorders such as AD, PD, and DLB are increasingly recognized as fluid rather than discrete, with substantial molecular and pathologic overlap. Additionally, different isoforms and conformers of these misfolded proteins appear to be associated with distinct disease phenotypes. This growing understanding of protein heterogeneity and co-pathology suggests that mixed pathology is the norm rather than the exception in neurodegenerative diseases.[79] Table 3 highlights key omics studies investigating the relationship between AD and other co-pathologies discussed below.

LB pathology staging can be categorized into Parkinsonism-associated brainstem/midbrain pathology[80] and cognitive dysfunction-associated limbic/neocortical pathology.[81] LB pathology is also commonly observed in the amygdala and olfactory regions. When considered the primary pathological feature, LB pathology is characteristic of PD and DLB. AD-type pathology is common in these conditions, making the delineation of whether a mixed pathology profile is a secondary AD or DLB challenging.[82] The prevalence of LB pathology in a sporadic AD context is estimated at ≈ 35%.[83,84] LB pathology, particularly the amygdala-predominant presentation, is common in autosomal dominant inherited AD, with prevalence estimates at ≈ 60%.[85] Cortical LB pathology is strongly associated with the presentation of psychosis, in

TABLE 2 Available omics datasets to study NPS in AD.

Data source	Data types	NPS covered	Sample size	References
Psych-AD	snRNA-seq DLPFC, DNA methylation data DLPFC, genetic pleiotropy analysis; spatial transcriptomics for validation	Major consortium to understand molecular mechanisms that contribute to NPS in AD. Covers neurodegenerative and neuropsychiatric phenotypes.	Varies with study. For RNA-seq data, 3154	62,63
The Mount Sinai Neuropsychiatric Symptoms in AD (NPS-AD) Study	snRNA-seq DLPFC	Study to understand molecular mechanisms that contribute to NPS in AD.	1494	54
Multiomic approach to elucidate novel disease mechanisms and biomarkers for psychosis in AD (MOA-PAD)	DNA methylation and transcriptomic data DLPFC	Psychosis	233 AD and control patients	43
National Alzheimer's Coordinating Center (NACC)	NPS phenotypes defined in Uniform Data Set structure; genomic array and sequence data (GWAS, WES/WGS)	NPS phenotypes: network structure of NPS in older adults with MCI and AD; courses of NPS and rate of functional decline	Varies depending on phenotype. More than 52,500 participants with NACC data.	29,64
UK Biobank	Psychiatric symptom phenotypes (not AD linked), genetic data, plasma, proteomic data	Multiple psychiatric phenotypes including depression and depressive symptoms —but important to consider sampling and comparison to other datasets.	Varies depending on phenotype. More than 500,000 participants,	65,66,67
AllofUS	Psychiatric symptom phenotypes (not AD linked), genetic data	Multiple NPS phenotypes including depression and depressive symptoms but important to consider sampling and comparison to other datasets.	Varies on phenotype. More than 312,000 participants	68
Study of shared mechanisms across the major psychiatric and neurodegenerative diseases.	Genetics, human brain transcriptomics, and proteomics	Eight psychiatric traits: MDD, BD, schizophrenia, anxiety, PTSD, alcoholism, neuroticism, and insomnia; five neurodegenerative diseases: AD, LBD, FTD, ALS, and PD	888 human brain transcriptomes, 722 human brain proteomes	57 Data available at: https://www.synapse.org/Synapse:syn31822992/wiki/617907
The Case Western MindPhenome Knowledge Base (MindPhenomeKB)	Knowledge Base derived using natural language processing to develop data-driven approaches to studying AD and associated neuropsychiatric disorders	Includes cognitive impairment, memory loss, brain atrophy, syncope, delusion, depression, aphasia, and others		69,70
GTEx v10	Resource of tissue and cell-specific gene expression and regulation across individuals	No specific NPS. eQTL analysis available for many tissues	946 samples, 19,788 RNA-seq samples	71,72,73 https://gtexportal.org/
brainSCOPE	Population-scale, single-cell resource for human brain: snRNA-seq and snATAC-seq data and gene regulatory analysis	Schizophrenia, BD, ASD, and AD	388	74
Brains for dementia research	NPS phenotypes, genetic data	Includes all forms of dementia and controls. NPI data and depression rating scales.	3276	75
HUNT health and memory study	NPS phenotypes, genetic data	NPI ratings on participants with all-cause dementia, many of whom lived in care home facilities	620	76

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; ASD, autism spectrum disorder; BD, bipolar disorder; DLPFC, dorsolateral prefrontal cortex; eQTL, expression quantitative trait locus; GWAS, genome-wide association study; LBD, Lewy body dementia; MCI, mild cognitive impairment; MDD, major depressive disorder; NPI, Neuropsychiatric Inventory; NPS, neuropsychiatric symptoms; PD, Parkinson's disease; PTSD, post-traumatic stress disorder; snRNA-seq, single-nucleus RNA sequencing; WES, whole-exome sequencing; WGS, whole-genome sequencing.

TABLE 3 Summaries of key studies using omics methods to examine the relationship between AD and other neuropathologies.

Study	Omics methods	Overall approach	Major findings
Shade, L.M.P. et al. (2024)[122]	GWAS	Examined GWA of genetic loci in 11 AD and related dementias neuropathology endophenotypes with participants from the National Alzheimer's Coordinating Center, the Religious Orders Study and Rush Memory and Aging Project (ROSMAP), and the Adult Changes in Thought study.	Identified seven associated loci with significant association, including three novel loci: *COL4A1*, *LZTS1*, and *APOC2*; 19 previously identified AD GWAS loci were associated with one or more neuropathologies. Cerebral cortex methylation proximal to *APOC2* was associated with cerebral amyloid angiopathy.
Shireby, G. et al. (2022)[116]	Methylomics, epigenome-wide association study	Conducted epigenome-wide association analysis of methylation for multiple AD neuropathology measures of cortical regions in 631 donors. Results were cross-referenced with previous DNA methylation studies. Additionally profiled DNA methylation in NeuN+ (neuronal-enriched), SOX10+ (oligodendrocyte-enriched) and NeuN−/SOX10− (microglia- and astrocyte-enriched) nuclei.	Identified differential methylation at 334 loci associated with AD pathology including loci not previously implicated in dementia. Differential methylation was primarily identified in non-neuronal nuclei. Highlighted a shared directionality in epigenomic profiles associated with tau and amyloid and those observed for co-pathological outcomes (TDP-43 and LB pathology measures).
Sanchez-Mut, J.V. et al. (2016)[123]	Methylomics	Analysis of DNA methylation patterns in prefrontal cortex samples of AD, PD, DLB, and AD-like neurodegenerative profile associated with Down syndrome compared to normal controls using whole-genome bisulfite sequencing.	Identified common aberrant CpG methylation changes across all disorders.
Bereczki, E. et al. (2018)[124]	Proteomics	Compared proteomic profiles of prefrontal cortex tissue of AD, PDD, DLB, and age-matched controls without dementia.	Identified 25 synaptic proteins with significantly altered levels in the disease groups. Decreases in *SNAP47*, *GAP43*, *SYBU* (syntabulin), *LRFN2*, *SV2C*, *SYT2* (synaptotagmin 2), *GRIA3*, and *GRIA4* were validated using ELISA or western blot. Cognitive impairment and rate of decline correlated with decreased levels of *SNAP47*, *SYBU*, *LRFN2*, *SV2C*, and *GRIA3*. Synaptic protein profiles varied significantly between disease and controls, as well as between AD and PDD, but not between AD and DLB, indicative of unique profiles between differing primary pathologies.
Olney, K.C. et al. (2025)[125]	Bulk transcriptomics	Bulk tissue RNA sequencing and differential expression analysis from anterior cingulate cortex samples of normal control, AD, DLB, and pathological amyloid cases with amyloid pathology but minimal or no tau pathology. DLB cases were subdivided into high Thal amyloid, Braak NFT, and low pathological burden cohorts. Used gene set enrichment and weighted gene correlation network analysis to identify pathways of differentially expressed genes.	Identified upregulation of genes involved in protein folding and cytokine immune response, and downregulation of fatty acid metabolism in DLB. Genes differentially regulated between AD and DLB showed strong enrichment of synaptic signaling, behavior and neuronal system pathways, with core inflammatory pathways shared between disease states. Sex-specific changes were identified in both AD and DLB.
Shwab, E.K. et al. (2025)[130]	Single-cell transcriptomics	Profiled the whole transcriptomes of cortical tissue from AD, PD, DLB, and normal control donors by snRNA-seq and used computational analyses to identify common and distinct differentially expressed genes, biological pathways, vulnerable and disease-driver cell subtypes, and alteration in cell-to-cell interactions.	The same vulnerable inhibitory neuron subtype was depleted in both AD and DLB. Potentially disease-driving neuronal cell subtypes were present in both PD and DLB. Cell–cell communication was predicted to be increased in AD but decreased in DLB and PD. DEGs were most commonly shared across NDDs within inhibitory neuron subtypes. The greatest transcriptomic divergence was observed between AD and PD, while DLB exhibited an intermediate transcriptomic signature.

(Continues)

TABLE 3 (Continued)

Study	Omics methods	Overall approach	Major findings
Tuddenham, J.F. et al. (2024)[131]	Single-cell transcriptomics	Single-cell RNA sequencing of microglia from donors with early-onset and late-onset AD, PD, MCI, ALS, FTD, PSP, DLBD, MS, HD, and stroke, as well normal controls, derived from a number of different brain regions. Performed differential expression analysis between microglial subtypes, compared proportions of subtypes in different disease groups, and examined enrichment of disease risk genes within subtypes. Also performed in situ and in vitro validations.	Identified microglial subtypes associated with antigen presentation, cell motility and proliferation, and a division between oxidative and heterocyclic metabolism. Specific subtypes were enriched for susceptibility genes of the diseases and the signature of disease-associated microglia. Found enrichment of risk gene expression for both AD and PD, but not for FTD/ALS, in two functionally implicated microglial subtypes.
Mathys, H. et al. (2023)[117]	Single-cell transcriptomics	snRNA-seq of prefrontal cortex nuclei from ROSMAP donors with a range of AD progression. Performed differential gene expression analysis in cell subtypes with regard to multiple measures of AD pathology, including LB and TDP-43 pathology, vascular pathology, medical conditions, and cognitive, physical, and social lifestyle variables.	Identified AD-pathology-associated altered gene expression between excitatory neuron subtypes, increase of the cohesin complex and DNA damage response factors in excitatory neurons and oligodendrocytes, and altered pathways associated with cognitive function, dementia, and AD resilience. Found selectively vulnerable somatostatin inhibitory neuron subtypes depleted in AD, and two inhibitory neuron subtypes with increased abundance in individuals with high late-life cognitive function. Identified a link between inhibitory neurons and AD resilience.
Gabitto, M.I. et al. (2024)[118]	Single-cell transcriptomics, single-cell epigenomics (chromatin accessibility)	snRNA-seq and snATAC-seq study of 84 individuals, used a multi-pathology pseudo-progression score, separating samples into early- and late-phase pathology profiles based on multiple measures of tau, amyloid, and cell composition.	Identified pseudoprogression-associated alterations in astrocyte and microglia function, remyelination responses in oligodendrocyte precursor cells, and neuronal subpopulations vulnerable to degeneration at both early and late stages, respectively. Notably, despite the inclusion of TDP-43 and LB pathology metrics in pseudoprogression score generation, they were minimally captured in this analysis.
Miyoshi, E. et al. (2024)[133]	Spatial transcriptomics, single-cell transcriptomics	Spatial transcriptomic (ST) and snRNA-seq analysis of late-onset sporadic AD and AD in Down syndrome (DSAD), and performed cell–cell communication analysis. Also performed spatial transcriptomics of an AD mouse model to identify cross-species transcriptomic changes.	Identified cortical layer-specific transcriptomic changes. Characterized an AD-risk associated glial inflammatory program dysregulated in upper cortical layers.

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; DEG, differentially expressed gene; DLB, dementia with Lewy bodies; DLBD, diffuse Lewy body disease; ELISA, enzyme-linked immunosorbent assay; FTD, frontotemporal dementia; GWAS, genome-wide association study; HD, Huntington's disease; LB, Lewy body; LBD, Lewy body dementia; MCI, mild cognitive impairment; MDD, major depressive disorder; MS, multiple sclerosis; NDD, neurodegenerative disorder; NFT, neurofibrillary tangle; NPS, neuropsychiatric symptoms; PD, Parkinson's disease; PDD, Parkinson's disease dementia; PSP, progressive supranuclear palsy; snRNA-seq, single-nucleus RNA sequencing; TDP-43, transactive response DNA binding protein 43 kDa.

particular visual hallucinations (VHs),[81] with potential interaction of AD and LB pathology severity in relation to VH presentation.[86–90] Agitation, aggression,[88,89,91] and depression[89,92–94] are also reported to be associated with LB pathology.

TDP-43 aggregates are pathological deposits exhibited in amyotrophic lateral sclerosis (ALS), AD, and FTD. They are observed in up to 57% of AD cases,[95] most frequently in the limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC) distribution,[95,96] affecting the amygdala at earlier stages and proposed to progress to the hippocampal, brainstem, and middle frontal gyrus regions.[97] This is at times accompanied with hippocampal sclerosis,[97] and TDP-43 is shown to colocalize with tau aggregates within neurons.[98] In the context of AD, LATE-NC is associated with worsening cognitive decline.[97] Behavioral changes, including symptoms such as delusions, disinhibition, and apathy, are common features in frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP), a disease bearing the same pathological aggregates. It is also reported as increased with AD LATE-NC pathology.[87,99] AD LATE-NC co-pathology has been associated with anxiety, disinhibition, apathy, personality change, aggression, and agitation symptoms.[89,91,100]

The presentation of AD pathology (NFT and Aβ), LB pathology, and LATE-NC together has been termed the quadruple misfolded protein (QMP) phenotype. Prevalence estimates of older individuals with dementia place the QMP at 12.3% and a further 38.1% estimate of individuals displaying three of the four proteinopathies.[101] Studies posit that the accumulation of multiple co-pathologies is the

norm in an aging brain,[102,103] with a consensus that a greater burden of co-pathology is associated with an additive worsening in disease burden.[104] The culmination of all pathologies, in particular the QMP phenotype, has been associated with a broad range of worsening neuropsychiatric symptoms, including psychosis, agitation, depression, anxiety, and apathy.[89]

In addition to the protein aggregate pathologies previously described, vascular co-pathology is also commonly observed. Cerebral amyloid angiopathy (CAA) sits at the intersection, describing the abnormal deposition of amyloid aggregates around the blood vessels of the brain. It is estimated to occur in ≈ 48% of AD cases and is associated with a broadly increased prevalence of a number of NPS.[105,106] Cerebrovascular disease (CVD), encompassing microinfarcts and arterio/atherosclerosis, is commonly observed in aged brains with AD pathology and shows an association with depression symptom presentation.[86,107]

3.2 | Genetics of co-pathology, shared pleiotropy, and growing resolution of specific risk

Genetic advances have provided interesting insights into the molecular underpinnings of co-pathologies in AD and crucial shared pathways in disease susceptibility. For example, the endo-lysosomal network genes *BIN1*, *TPCN1*, and *GRN* have been implicated in AD[108] and DLB.[109–111] Variants in *GRN* have also been implicated in FTD[112,113] and PD,[114] illustrating pleiotropic effects. Several genes linked to amyloid processing and clearance have also been associated with mixed AD and LB pathologies. These include *BIN1*, *APOE*, *APP*, *PSEN1*, and *PSEN2*,[115] emphasizing the close molecular relationships between AD pathological changes and LB disease.

With larger, pathologically characterized cohorts of AD (Table 4), genetic discovery analyses of multiple co-pathological endophenotypes have become viable.[116–121] In one such study, using 7804 samples, researchers meta-analyzed genetic associations with 11 pathological outcomes, encompassing all the previously mentioned co-pathologies.[122] They confirm a number of known AD-associated susceptibility loci and identify four novel loci with pathology-specific associations, including the CAA-associated *APOC2*. *APOC2* is a gene in close proximity to the *APOE* region, but its association to CAA was independent of *APOE* status. They highlight two DNA methylation sites as mQTL of the *APOC2* risk variant, significantly associated with CAA severity and expression of the *APOC2* transcript. This study shows the power of using distinct co-pathological outcomes to refine and uncover risk factors for AD, determining their potential causal pathological outcomes and providing mechanistic targets via additional layers of omic regulation.

3.3 | A multiomic perspective on co-pathology

The evidence of pleiotropy extends beyond implicated genetic risk loci. A DNA methylation study in AD *post mortem* cortical tissue of 631 donors[116] highlighted a shared directionality in epigenomic profiles associated with tau and Aβ and those observed for co-pathological outcomes (TDP-43 and LB pathology measures). This finding is similarly reported in other, lower-powered epigenomic studies of neurodegenerative diseases.[123] These, however, do not rule out pathology-specific epigenetic effects. For example, the sole TDP-43 pathology-associated methylation locus, residing near the gene *STK38L*, was not among those significantly associated with tau and Aβ pathology.[116]

Proteomic comparisons between differing neurodegenerative diseases have indicated similar shared and distinct profiles. In a study of 92 brain samples with AD, PDD, DLB, and control groups,[124] researchers reported levels of synaptic proteins that were able to discriminate AD from PDD but not from DLB, indicative of unique profiles between differing primary pathologies. Similar findings are reported from studies looking at the transcriptomic level, such as a recent analysis comparing DLB, AD, and normal controls.[125] DEG showed evidence of shared dysregulation of inflammation, immune response, microtubule dynamics, and neurotransmission between AD and DLB. Notably, genes related to synaptic signaling, ribosomes, and ubiquitin processing showed evidence of greater dysregulation in DLB compared to AD, suggesting potentially differentiating mechanisms.

Although outcomes such as microRNA (miRNA) expression have been highlighted for robust association with AD,[126] no studies to date have tested their association with co-pathologies within AD. In a recent study of 641 brain samples,[127] researchers identified 137 miRNAs with association to AD phenotypes, controlling for arteriosclerosis, atherosclerosis, CAA, LB, TDP-43, infarcts, and hippocampal sclerosis. Although these miRNAs can be interpreted as associated with AD without confounding co-pathology influence, the report does not go further to test the miRNAs associated with each distinct neuropathological endophenotype, an area warranting further research.

Many studies are now resolving omic measures down to the single-cell level,[128] revealing cell-specific signatures, relevant to disease susceptibility and resilience.[129] These studies are now beginning to compare the single-cell profile across differing neurodegenerative diseases. In an snRNA-seq comparison of AD, DLB, PD, and normal controls,[130] researchers have identified a subtype of inhibitory neurons with evidence of depletion in both AD and DLB, along with vulnerable neuronal cell types distinct to AD and PD. In a microglia-specific snRNAseq dataset,[131] including samples with AD, DLB, PD, and FTLD, although not performing direct inter-group comparisons, researchers report an enrichment for genetic risk for both AD and PD, but not for FTLD/ALS, in two functionally implicated microglial subtypes.

Few single-cell studies to date have primarily investigated co-pathological endophenotypes within AD. One study testing co-pathology outcomes, including LB, TDP-43, and vascular pathology, reported minimal gene expression association compared to primary measures of amyloid and tau.[117] Findings from an snRNA-seq and snATAC-seq study[118] of 84 individuals used a multi-pathology pseudo-progression score, separating samples into early- and late-phase pathology profiles based on multiple measures of tau, amyloid, and cell composition. Findings revealed pseudoprogression-associated

TABLE 4 Summary of cohorts selected for detailed quantified neuropathological assessment criteria covering measures of tau (Braak NFT), amyloid (Thal stage), neuritic plaque (CERAD), TDP-43, LB, CAA, and vascular (arteriosclerosis, atherosclerosis, infarcts), and with available multiomic datasets.

			Data availability														
			Genetic			Bulk epigenetic			Bulk gene expression						Single nucleus and spatial		
Study cohort	Total N*	Citations	Genotyping array	WGS	Methylation array	ChIPseq	ATACseq	RNAseq	sRNAseq	circRNAseq	Proteomics	Metabolomics	Lipidomics	snATACseq	snRNAseq	Spatial
Religious Orders Study and Rush Memory and Aging Project (ROSMAP)	>3322	117,119	X	X	X	X	X	X	X			X		X	X	
Brains for Dementia Research (BDR)	>1200	116,120	X		X											
Knight-Alzheimer Disease Research Centre (Knight-ADRC)	6625	121	X	X	X			X	X	X		X	X		X	X
Seattle Alzheimer's Disease Brain Cell Atlas (SEA-AD)	84	118	X					X						X	X	X

Notes: Data are summarized by total *n* for donors and summarized for the availability of specific multiomic outcomes quantified. Spatial methods refer to MERFISH for SEA-AD and Vizgen for Knight-ADRC. For further information, refer to study publication.

Abbreviations: ATACseq, assay for transposase-accessible chromatin with sequencing; CAA, cerebral amyloid angiopathy; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; ChIPseq, chromatin immunoprecipitation sequencing; circRNAseq, circular RNA sequencing; LB, Lewy body; NFT, neurofibrillary tangle; snATACseq, single nucleus ATAC sequencing; sRNAseq, small RNA sequencing; WGS, whole genome sequencing; TDP-43, transactive response DNA binding protein 43 kDa.

*N is for full study inclusion and does not refer to coverage of every single outcome listed.

alterations in astrocyte and microglia function, remyelination responses in oligodendrocyte precursor cells, and neuronal subpopulations vulnerable to degeneration at both early and late stages, respectively. Notably, despite the inclusion of TDP-43 and LB pathology metrics in pseudoprogression score generation, they were minimally captured in this analysis. In both cases, negative results may be a result of low coverage of particular pathologies in available datasets and warrant further investigation.

Spatial omics have begun to allow insight into the molecular environment relating to specific pathologies in AD, for example finding glial inflammatory gene networks related to amyloid plaque proximity.[132,133] Notably, a recent spatial transcriptomic study of LB pathology[134] and a transcriptomic study of neuronal populations affected by NFT pathology[135] highlighted a similar profile of cortical neuron vulnerability but also vulnerable neuronal subtypes and molecular alterations distinct to each pathology.

In summary, there is a growing appreciation that co-pathologies appear to be a feature, rather than an exception in AD and we have evidence of their explaining certain aspects of clinical heterogeneity. There is strong evidence of a shared profile across multiple pathologies, along with a growing resolution of profiles unique to differing pathologies. These findings have the potential for a more refined, personalized approach to AD clinical management, determined by individual patients' distinct pathological profiles. These studies also have important connotations for therapeutics in AD, indicating that effective therapeutics for primary AD-associated tau and amyloid pathologies may not be efficacious in addressing common co-pathologies. Further work is needed, addressing the specificity of associated profiles to differing pathological outcomes, to help inform multifaceted treatment approaches.

4 | SEX DIFFERENCES IN AD

4.1 | Overview of sex differences in AD

Sex differences in AD have been long documented, and it is estimated that two thirds of patients with AD at any given time are women.[136] To

some extent, this elevated prevalence may reflect survival effects, as women typically outlive men, and AD advances with age, but incidence rates suggest additional mechanisms as well.[137] Possible mechanisms that may explain the increased prevalence in women include genetic factors, such as X chromosome-linked genes and *APOE* ε4, which have greater effects in women relative to men.[138] Women also have a higher frequency of depression[139] and lower average levels of education relative to men,[140] both of which are AD risk factors. Finally, women have hormonal changes during pregnancy and menopause, which may play a contributory role.[141] Data also suggest that women may display lower resilience to AD pathology and cognitive decline relative to men in terms of more rapid progression to both mild cognitive impairment (MCI) and dementia,[142] in which *APOE* ε4 may play a contributory role. AD pathology has also been shown to differ between the sexes. According to a study focusing on clinicopathologic differences between men and women with AD,[143] each unit increase in AD pathology resulted in a 3-fold increase in clinical AD in men but a > 20-fold increase in clinical AD in women. This striking disparity suggests that women exhibit greater clinical symptoms of AD pathology compared to men, even at similar levels of underlying pathology. Another study[144] demonstrated that while Aβ levels showed only a borderline difference between women and men, women had higher levels of global AD pathology and tau tangle density after adjusting for age and education. This observation has been corroborated by subsequent studies.[145,146]

Recent data have suggested that there may be important sex differences in the prevalence and domain constitution of NPS in women compared to men.[147] According to a recent meta-analysis, NPS domains of AD patients differed by sex: men displayed more severe apathy and agitation, while women showed greater symptoms of depression and psychosis.[147,148] Another recent study found a higher prevalence of NPS among female *APOE* ε4 homozygotes compared to heterozygotes and non-carriers among individuals with AD or with risk for AD, while no such differences were observed in males,[149] suggesting that *APOE* ε4 may play a possible modulatory role in NPS. A separate study from the same group using a neuropathological sample found a similar pattern for psychosis, particularly in the cohort with LB pathology.[150]

Anti-amyloid therapies have emerged as important breakthroughs in AD treatment in recent years. While most studies have not explicitly examined sex-specific differences in treatment efficacy,[151] preliminary observations suggest that these therapies may exhibit differential efficacy between sexes.[152,153] However, further large-scale studies are required to determine whether this is the case and to explore the underlying mechanisms.[153] Table 5 highlights key omics studies discussed below investigating the interaction between sex and AD.

4.2 | Examining sex differences in AD genetic risk loci

Recent genomics studies are increasingly reporting sex differences in AD. As alluded to above, the *APOE* ε4 allele has long-standing and compelling support for stronger effects on AD risk, memory decline, and tau pathology in women.[1–5] At the genome-wide level, a prior review[154] highlighted sex-differentiated AD-correlated genetic loci, which have tended toward female-specific associations. Subsequent studies, in still relatively small samples ($N < 30{,}000$), corroborated this female tendency of sex-differentiated genetic associations with AD prevalence, pathology, and resilience.[155–158] While sex-specific genetic risk factors remain somewhat scarce, larger-scale sex-stratified AD GWAS are on the horizon and should provide additional important insights.[159] It is relevant to emphasize that the X chromosome has been understudied in AD genetics due to its inherent technical and analytical challenges, despite it being an obvious potential source of sex differences.[160] Approximately 70% of X chromosome genes in women undergo random inactivation to balance expression relative to men, while the remaining genes show variable escape from inactivation, contributing to sex differences in disease pathway expression.[161–163] Recently, the first large-scale X chromosome-wide association study of AD ($n = 1{,}152{,}284$) revealed four genes with evidence for escape from X chromosome inactivation, suggesting they may contribute to female-specific AD pathways.[164] Additionally, hormonal factors are relevant to AD and may interact with genetic risk.[142,165,166] miDNA abundance has also been implicated in AD, with evidence of larger abundance in pre-menopausal women compared to men.[167,168] Altogether, these research avenues are highly promising to help elucidate sex differences in AD genomics.

4.3 | Integration of genomic mapping and other omics in analyzing AD sex differences

Beyond genomics, other types of omics data (e.g., transcriptomics, proteomics) can also be used to directly glean insights into sex differences in the molecular heterogeneity of AD. In isolation, such approaches are effective in identifying genes and pathways associated with AD, and may aid in the identification of novel biomarkers,[169,170] but are less effective in identifying disease-causal factors. However, integration of omics data with genetic data enables QTL mapping to study the genetic factors regulating omics-derived AD-associated molecular features.[171] Omics and mapping data can be further integrated with GWAS to identify genetic variants influencing expression of a given molecular feature that also consistently associate with AD risk.[172] This approach, termed according to the integrated omics layer—such as transcriptome-wide or proteome-wide association study (TWAS or PWAS)[172–174]—has the advantage of increased power when combining multiple "sub-threshold" signals and informs on likely causal genes, but has the downside of being restricted to molecular features that are genetically regulated.

With regards to omics-driven insights into AD sex specificity, there is mounting evidence that epigenetic aging may differ in males and females. In a recent study using the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset, it was observed that females exhibited accelerated epigenetic aging compared to males.[175] By contrast, studies done in healthy older adults seem to favor accelerated aging among males.[176] The X chromosome may play an important modulatory role in AD, as women possess two X chromosomes (one paternal and one

TABLE 5 Summaries of key studies using omics methods to examine the relationship between sex and AD.

Study	Omics methods	Overall approach	Major findings
Eissman, J.M. et al. (2024)[156]	GWAS	Performed sex-stratified and sex-interaction GWAS in non-Hispanic black and non-Hispanic white participants using harmonized memory composite scores from four cohorts of cognitive aging and AD.	Identified three memory-associated sex-specific loci, including one X-chromosome locus. Heparan sulfate signaling was identified as a sex-specific pathway, and sex-specific correlations with memory were identified for education, cardiovascular, and immune patient traits.
Dumitrescu, L. et al. (2019)[155]	GWAS	Performed sex-stratified GWAS to identify genetic associations with AD endophenotypes from six brain bank data repositories. AD-associated loci were assessed for sex interactions. Follow-up analyses took into account age at onset and cognitive, neuroimaging, and CSF endophenotypes.	A chromosome 7 locus had NFT association in males but not females. This locus was also associated with hippocampal volume, executive function, and age-at-onset in males.
Deming, Y. et al. (2018)[157]	GWAS	Sex-stratified and sex interaction genetic analysis of CSF biomarkers. Evaluated sex interactions at previous GWAS loci, and performed GWAS to identify sex-specific correlations. Examined sex-specific associations between PFC gene expression at correlated loci and plaques and NFTs using autopsy data from the ROSMAP.	For Aβ42, identified sex interactions at loci proximal to the *SERPINB1* and *LINC00290* gene regions, with stronger associations for females compared to males. PFC pre-regulation of *SERPINB1*, *SERPINB6*, and *SERPINB9* correlated with increased amyloidosis among females but not males. For total tau, sex interaction was identified proximal to *GMNC* with stronger association in females than males. Sex-specific association of this locus was also identified for NFT density at autopsy for females but not males.
Eissman, J.M., et al. (2022)[158]	GWAS	Used large-scale genomic data for AD resilience from four cohorts of cognitive aging, amyloid PET data from two cohorts, and amyloid neuritic plaque burden data across two cohorts to construct resilience phenotypes. Performed sex-stratified and sex-interaction GWAS and pathway analysis to identify genetic factors associated with AD resilience in a sex-specific manner.	Identified a chromosome 10 locus associated with higher AD resilience in females. This locus was situated within chromatin regions interacting with RNA processing gene promoters, including GATA3. Genetic correlation analysis identified female-specific association between AD resilience and frontotemporal dementia and male-specific associations with variable heart rate. Resilient females were found to have lower susceptibility to MS, while resilient males had higher susceptibility.
Belloy, M. et al. (2024[164]	XWAS (X-chromosome genetic association), transcriptomics, pQTL mapping	Meta-analysis of X-chromosome genetic association of AD in case–control, family-based, population-based, and longitudinal AD-related cohorts from the US Alzheimer's Disease Genetics Consortium, the Alzheimer's Disease Sequencing Project, the UK Biobank, the Finnish health registry, and the US Million Veterans Program. Risk of AD was evaluated through case–control logistic regression analyses. Genetic data available from high-density single-nucleotide variant microarrays and whole-genome sequencing, and summary statistics for multi-tissue expression and protein quantitative trait loci available from published studies were included, enabling follow-up genetic colocalization analyses. Analyses included European and African ancestry participants.	Six independent loci passed X chromosome–wide significance, with four showing support for links between the genetic signal for AD and expression of nearby genes in brain and non-brain tissues. One of these four loci passed conservative genome-wide significance, with its lead variant centered on an intron of SLC9A7, which regulates pH homeostasis in Golgi secretory compartments and is anticipated to have downstream effects on Aβ accumulation.
Inkster, A.M. et al. (2022)[175]	Methylomics	Used data relating to epigenetic age acceleration metrics from the ADNI database to examine associations between epigenetic age acceleration, cognitive impairment, sex, and AD risk biomarkers.	Females were found to exhibit accelerated epigenetic aging with regard to the transition from normal cognition to cognitive impairment than males.
Phyo, A.Z.Z. et al. (2024)[176]	Methylomics	Epigenetic clocks (HorvathAge, HannumAge, PhenoAge, GrimAge, GrimAge2, and DunedinPACE) were estimated in blood from participants ≥ 70 years of age. A system-wide deficit accumulation frailty index was generated, consisting of 67 health measures. Brain-predicted age differences (brain-PAD) were estimated based on neuroimaging.	Epigenetic age acceleration was reduced in females compared to males, but females had higher frailty indexes, and there was no difference in brain-PAD between the sexes.

(Continues)

TABLE 5 (Continued)

Study	Omics methods	Overall approach	Major findings
Caceres, A. et al. (2020)[185]	Bulk transcriptomics	Examined chromosome Y gene expression in 13 undiseased brain regions and blood using data from the Genotype-Tissue Expression (GTEx) project to identify individual propensity for chromosome Y dysregulation across multiple tissues. Subsequently analyzed AD risk associated with extreme chromosome Y downregulation (EDY) and its interaction with age, using publicly available data from four transcriptomic studies of AD in brain tissue and in one of AD in blood.	EDY co-occurred across multiple brain regions and associated genetic loci within ACSS3/PPFIA2, previously linked to Ab. A significant interaction of EDY with age was identified. Results suggest EDY avoidance promotes AD resilience.
Guo, L. et al. (2023)[191]	Bulk transcriptomics, single-cell transcriptomics	Performed multiscale network analysis of AD brain transcriptomic from MSBB and ROSMAP cohorts to identify disease drivers with sexually dimorphic expression patterns. Expression patterns of a top sex-specific AD driver network were validated using human brain samples and AD mouse models.	LRP10 was identified as a top driver of sex differences in AD. EFAD mouse models indicated that LRP10 had sex-dependent effects on cognitive function and AD pathology, neurons, and microglia most affected. snRNA-seq of mouse brains indicated LRP10 as a key network regulator of AD in females. Yeast two-hybrid screening identified eight LRP10 binding partners.
Lopez-Cerdan, A. et al. (2020)[193]	Bulk transcriptomics	Tissue-specific meta-analyses were conducted using data from transcriptomic studies of AD. A comprehensive functional characterization was then performed, focusing on the cortex due to the presence of significant sex-dependent transcriptomic alterations. This included exploration of biological pathways using protein–protein network interaction and over-representation analyses and estimation of transcription factor activity via VIPER analysis.	Female AD patients showed more differential gene expression than males. DEGs were grouped into six subsets according to expression in female and male AD patients. Subset I (female repressed genes) showed significant results during functional profiling. More significant impairments in pathways related to synapse organization, neurotransmitters, protein folding, Aβ aggregation were identified in female compared to male AD patients.
Paranjpe, M.D. et al. (2021)[194]	Bulk transcriptomics	Meta-analysis of gene expression data from seven independent datasets of age-matched AD and normal control brains and blood samples. Gene-based, pathway-based, and network-based approaches were used to identify sex-specific gene expression patterns. A linear support vector machine model was used to assess the efficacy of a sex-specific AD gene expression signature in distinguishing AD from controls.	An immune signature in the brain and blood of female AD patients but absent in males was consistently identified through gene-expression, network analysis and cell type deconvolution approaches. Network-based analysis identified female-specific coordinated expression of genes modulated by the presence of the *APOE* ε4 allele.
Davis, E.J. et al. (2021)[195]	Bulk transcriptomics	Examined X chromosome differential gene expression in the dorsolateral prefrontal cortex of AD patients and normal controls using bulk RNA-seq data obtained from the ROSMAP cohorts. Analyzed the association of X chromosome gene expression with NFT burden in women and men.	Expression of X chromosome genes was significantly associated with cognitive change in women but not in men. Upregulation of a majority of differentially expressed X chromosome genes was associated with slower cognitive decline in women, while expression of several genes was correlated with tau burden in men.
Maffioli, E. *et al.* (2022)[196]	Bulk transcriptomics, metabolomics	Investigated sex-dependent changes in the molecular composition of hippocampus samples from AD patients and normal controls using an integrated omics approach including bulk transcriptomics, proteomics, and metabolomics.	Strong metabolic differences were identified between control and AD male and female cohorts. Decreased insulin response was observed in females compared to males, and serine metabolism was also modulated in a sex-dependent manner. Overall, AD was found to strongly alter sex-specific proteomic and metabolomic profiles.
Hou, Y. et al. (2024)[197]	Bulk transcriptomics, proteomics, metabolomics	Characterized cellular metabolism and immune response endophenotypes across AD donors with respect to sex using ROSMAP bulk transcriptomic and metabolomic data. Comparison was made across a range of clinical diagnostic and cognitive status metrics.	Identified sex-specific metabolic pathways associated with the AD, including elevation of AD inflammatory metabolites involved in interleukin (IL)-17 signaling, C-type lectin receptor, interferon signaling, and Toll-like receptor pathways in females. Also characterized sex-specific microglial immunometabolism endophenotypes, and observed diminishment of glutamate-mediated communication between excitatory neurons and microglia in females.

(Continues)

TABLE 5 (Continued)

Study	Omics methods	Overall approach	Major findings
Do, A.N. et al. (2024)[199]	Proteomics	Used protein-targeting aptamers to examine sex-specific CSF proteomic signatures of amyloid/tau-positive AD cases and normal controls.	Identified male- and female-specific CSF proteomic variations that strongly predicted amyloid/tau positivity. Male-specific proteins were associated with postsynaptic and axon-genesis and were enriched in astrocytes and oligodendrocytes, with *PTEN*, *NOTCH1*, *FYN*, and *MAPK8* as network hubs. Female-specific proteins were associated with cytokine activity and were enriched in neurons, with JUN, YWHAG, and YWHAZ as network hubs.
Belonwu, S.A. et al. (2021)[200]	Single-cell transcriptomics	Used snRNA-seq data to examine sex-stratified differential gene expression and pathway network enrichment in human prefrontal and entorhinal cortex AD and normal control samples at the cell-type level.	Identified sex differences in AD primarily in glial cells of the prefrontal cortex. In the entorhinal cortex, the same genes and networks were perturbed in opposite directions between sexes in AD vs. controls.
Coales, I. et al. (2022)[201]	Bulk transcriptomics, single-cell transcriptomics	Used bulk and snRNA-seq from AD and normal control human *post mortem* microglial nuclei, peripheral monocytes, monocyte-derived macrophages, and induced pluripotent stem cell-derived microglial-like cells.	Expression of AD risk genes and proinflammatory immune responses genes was enriched in microglia from normal control females relative to males, as well as in peripheral monocytes isolated from postmenopausal women and in monocyte-derived macrophages obtained from premenopausal women relative to age-matched males.
Zhang, L. et al. (2021)[204]	Methylomics	Large-scale meta-analysis of sex-specific DNA methylation differences in AD. Uses data from four epigenome-wide AD association studies of prefrontal cortex brain samples. Used a sex-stratified analysis examining methylation–Braak stage associations separately in males and females, and an analysis of sex interaction with methylation–Braak stage association magnitude.	Identified 14 novel sex-specific, AD Braak stage associated CpGs, mapped to genes including *TMEM39A* and *TNXB*. Methylation changes of previously AD-associated genes, including *MBP* and *AZU1*, were also shown to be predominately associated with only one sex. Methylation differences were enriched in biological pathways including integrin activation in females and complement activation in males.

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; *APOE*, apolipoprotein E; CSF, cerebrospinal fluid; CT, computed tomography; DEG, differentially expressed gene; GWAS, genome-wide association study; MS, multiple sclerosis; MSBB, Mount Sinai Brain Bank; PET, positron emission tomography; PFC, prefrontal cortex; NFT, neurofibrillary tangle; ROSMAP, Religious Orders Study and Memory and Aging Project; snRNA-seq, single-nucleus RNA sequencing.

maternal), while men only possess a single maternally-derived X chromosome. An extra X chromosome, but not the maternal X chromosome alone, is associated with increased expression of genes that escape X inactivation, potentially providing protective effects against AD.[177,178] A recent murine model study suggests that aging triggers partial reactivation of genes on the inactive X chromosome in the female mouse hippocampus, including *Plp1*, a myelin-associated gene, and that this reactivation may contribute to female resilience against brain aging.[179] Such studies may explain why women tend to live longer with AD than men[180,181] despite exhibiting higher levels of AD pathology at autopsy.[182]

The Y chromosome may also contribute to sex differences in AD. For instance, loss of the Y chromosome (LOY), the most common acquired mutation in aging men,[183] is associated with a higher susceptibility to AD.[184] A further study analyzing five transcriptomic datasets[185] found that extreme downregulation of the Y chromosome significantly interacts with age and is linked to AD. Taken together, these studies suggest that the Y chromosome may contribute to protective mechanisms in males, and its loss or dysregulation could exacerbate AD risk and progression.

Menopause and other hormonal changes associated with aging in women may play an important role in DNA methylation and epigenetic aging.[186] In terms of transcriptomics, the Genotype-Tissue Expression (GTEx) project has revealed widespread evidence of sex-heterogeneous gene expression across the human body, with approximately one third of all genes having sex-biased expression in at least one tissue.[187] These observations held across the autosomes and X chromosome and tended to be tissue specific, notably including brain tissues as corroborated by other recent human studies,[188,189] with small effects in various biological pathways. Recent studies have reported sex-specific AD-related gene expression changes across different brain areas in humans and rodents,[190–194] with an apparent tendency for female discoveries. X chromosome-specific analyses in the human brain have also pointed to gene expression associations with cognition and AD pathology.[195] By integrating human brain transcriptomics and metabolomics data across AD individuals, one study found a decrease in insulin or modulated serine metabolism signatures when comparing the female to the male group,[196] while another study observed sex-differentiated microglial immunometabolism characterized by decreased glutamate metabolism and elevated interleukin-10

signals in female patients.[197] Insights into proteomic sex differences are still relatively scarce, but a recent large-scale human brain study[189] determined that 13.2% of studied proteins had sex-differentiated abundance. In the human cerebrospinal fluid (CSF) of healthy, older individuals, ≈ 80% of studied proteins showed age- and sex-related effects,[6] while in plasma two thirds of proteins differed significantly by sex.[198] In terms of AD-related observations, CSF proteomic analyses identified close to 500 sex-specific proteins associated with amyloid and tau pathology status.[199] Cell-specific transcriptomic data have also corroborated AD sex differences, with an initial study in the human prefrontal cortex showing that female cells were overrepresented in AD-associated cell subpopulations and that ranscriptional responses differed substantially between sexes,[200] and subsequent studies extending concordant insights.[201] There are numerous other examples of omics-based observations of sex differences in AD, with many summarized in two recent reviews by Lopez-Lee *et al.*[202] and Guo *et al.*[203] These highlight the importance of sex chromosomes versus sex hormones and interactions between sex and *APOE ε4* across omics layers, and note some prominent emerging sex-differentiated pathways, including metabolism and immunity. Notably, Guo *et al.* provide an in-depth overview of published omics datasets and the related insights they provided, summarizing that > 75% of selected omics studies identified female-specific changes.

When using genetic data to map QTLs, the study of sex differences is still relatively rare, and current findings suggest less obvious sex differentiation. For mQTLs, it appears that < 5% of those studied show evidence of sex-specific effects.[204,205] Similarly, the GTEx project and Wingo *et al.*[189] indicated that no sex-biased eQTLs passed standard false discovery rate–corrected *P* values < 0.05, while only 1.5% of studied proteins in Wingo *et al.* showed sex-biased protein (p)QTLs.[189] Similarly, a large sex-stratified plasma proteomics study in the UK Biobank observed < 100 sex-biased pQTLs (< 5% of studied proteins).[198] At the single-cell level, there are, to our knowledge, no sex-stratified eQTL studies yet, but it is only since very recently that sample sizes are becoming large enough to merit such analyses without sex stratification.[206,207] The limited detection of sex-biased QTLs should be considered with the knowledge that gene-by-environment interactions are notoriously challenging to detect, that individual variant sex-specific effects may be small and reside at subthreshold levels, and that many of the listed studies would benefit from additional power. As noted earlier, QTL studies can be integrated with GWAS through approaches such as PWAS or TWAS. This is particularly compelling moving toward integration with sex-stratified GWAS, where Wingo *et al.*[189] already demonstrated some first successes with sex-stratified PWAS across different traits, including AD. With the increasing size and quality of sex-stratified GWAS, such approaches are likely to generate important novel insights into AD sex differences.

Emerging data on sex-related differences across omics layers have the potential to be transformative. By characterizing sex-related variables that provide resilience or lead to increased disease susceptibility, advancements in omics research into AD sex differences may help identify sex-specific mechanisms of disease that will facilitate the development of new strategies for sex-specific AD prevention and treatment, with earlier diagnosis through the discovery of novel biomarkers, personalized interventions through the identification of patient-specific drug targets, and enhanced clinical outcomes for both sexes.

5 | CONCLUDING REMARKS, PERSPECTIVE, AND FUTURE DIRECTIONS

In this article, we have highlighted the utility of multiomics approaches to the exploration of AD heterogeneity and disease subtypes. We demonstrated the importance of integrative multiomics studies in dissecting the multifactorial and complex nature of AD molecular etiologies (Figure 1, upper and middle panels). Characterizing the diverse multiomic profiles in tissues from AD patients is imperative for progressing toward the development of precision medicine strategies for the treatment and prevention of AD as a group of diseases. Ultimately, the work reviewed here has translational implications in multiple ways toward precision medicine in AD, including the development of biomarkers and therapeutics targets, and the design and implementation of clinical trials (Figure 1, lower panel). First, the multiomics datasets hold a valuable utility in the development of genetic and molecular biomarkers. For example, transfer from validated transcriptomic signatures will facilitate the refinement of CSF and blood[208] biomarkers, and will improve the precision of risk prediction for early pre-clinical diagnosis of AD in individuals of diverse backgrounds. The work reviewed here demonstrates numerous examples of genes, their protein isoforms, and biological pathways that contribute to phenotypic variability (comorbidity with particular NPS and/or co-pathologies) among specific groups of patients (e.g., women or men) that can be translated into more accurate diagnostic biomarkers and therapeutics targets, stratified by patient sub-groups. It is imperative for future work to expand these investigations to additional patient groups, such as those of different ancestral backgrounds, to further tailor biomarker and therapeutics applications. Second, these new biomarkers will be essential for clinical trials, primarily by providing indicative and measurable readouts to enable accurate and precise monitoring of disease progression for the assessment of drug efficacy and evaluation of treatment response. Moreover, such biomarkers will improve the design of clinical trials by identifying the patient populations likely to benefit from the investigational new treatment (patient selection), accounting for ancestry, sex, and other risk factors of the individual patient. Third, the discovery of gene-, allele-, transcript isoform–, and cell type–specific drug targets will offer the opportunities to develop new and more effective therapeutics to treat, delay, and/or prevent AD with consideration of the individual patient attributes. Collectively, multiomics knowledge enhances the development of precise and accurate medicine for AD (Figure 1, lower panel).

An additional major gap in the study of the genetics and molecular underpinnings of AD and related dementias, beyond those discussed in detail above, is ancestral diversity, as most genetics and functional genomics studies have been conducted in subjects from European ancestry, while other populations are largely understudied. Evidence

of differential disease risk across populations of diverse ancestry raises important questions related to the extent of shared and distinct genetic etiologies and molecular phenotypes across these populations. Thus, the use of omics studies in tackling these questions, including GWAS and QTLs based on populations with diverse ancestral backgrounds, is vital for the mechanistic understanding of AD across various demographic groups, as well as the translation of these findings into personalized treatment strategies with respect to ancestral genetic background. Additional facets of population diversity with known influence on AD, such as geographic location, socioeconomic status, education level, social engagement, and so forth, also warrant further study. Promoting and extending AD research to include understudied diverse populations is a high priority, as personalized medicine in AD and related dementias may prove more effective.

Understanding the differences in AD between patients from varying demographic categories is important. Additionally, it is also crucial to obtain deeper insights into the complexity of AD within individual cases, including disease stage, rate of progression, and response to medications. In addition to examining gene expression levels through short-read RNA-seq, long-read sequencing technologies[209] can expand the capacity of transcriptomic data to identify AD-associated changes in RNA splicing within specific tissues at the single-cell level, which could potentially enable the future development of treatment strategies specifically targeting disease-associated splice variants.[210] Moreover, understanding early changes in brain regions involved in disease prior to neurodegeneration is imperative, and can be facilitated by integration of multi-omic methods in studying single-cell and spatial omics of post-autopsy tissues from early disease stages and younger at-risk individuals, based on criteria such as family history and genetic factors (e.g., *APOE*, *PRS*), as well as studying biofluids (i.e., CSF and plasma) of living donors from high-risk populations. Molecular phenotypes based on omics profiles would help trialists and clinicians to characterize and classify individual AD cases with a high degree of precision, and by that advance future drug development and patient care regimens.

As is evident from the diverse disease aspects we specifically focused on in this review, rather than a monolithic disease, AD may represent multiple disease subtypes characterized by a complex range of comorbid clinical symptoms and co-pathologies. This is reflected in the recent development of new diagnosis and staging strategies integrating both biomarker and clinical data for AD as well as other neurodegenerative diseases,[211–215] in an effort to better account for this complexity in the diagnostic process. Furthermore, recent studies have suggested definitions of specific AD subtypes. Pathologic factors have been used to delineate four major subtypes of AD,[216] while at least five separate molecular subtypes have been identified using CSF proteomics.[217,218] Integration of multiple omics datasets, including transcriptomic, epigenomic, proteomic, metabolomic, and lipidomic profiles via machine learning has also been used to define multiple AD subtypes,[219,220] which have been subsequently linked to distinct NPS profiles.[221] Moreover, NPS such as psychosis may themselves be markers of a distinct underlying biology.[43] However, as discussed above, the heterogeneity of AD is highly multifactorial, and the examination of individual variables in isolation is insufficient to capture the full spectrum of AD variability. Because of this heterogeneity, there is no single "silver bullet" to fight AD and related dementias. Thus, ongoing and emerging studies integrating forefront genomic technologies and methods to enrich the molecular datasets provide a framework for the development of precision medicine strategies tailored to the treatment of individual patients with respect to the full range of complexity in AD.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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