HHS Public Access

Author manuscript

Biol Psychiatry. Author manuscript; available in PMC 2023 January 01.

Published in final edited form as:

Biol Psychiatry. 2022 January 01; 91(1): 61–71. doi:10.1016/j.biopsych.2021.02.968.

Sex Differences in Alzheimer's Disease: Insights From the Multiomics Landscape

Lei Guo,
Department of Genetics and Genomic Sciences, Mount Sinai Center for Transformative Disease Modeling, Icahn School of Medicine at Mount Sinai

Margaret B. Zhong,
Department of Neuroscience, Barnard College of Columbia University, New York

Larry Zhang,
Department of Neurology, Icahn School of Medicine at Mount Sinai; Research and Development Service, James J. Peters VA Medical Center, Bronx, New York.

Bin Zhang,
Department of Genetics and Genomic Sciences, Mount Sinai Center for Transformative Disease Modeling, Icahn School of Medicine at Mount Sinai

Dongming Cai
Department of Neurology, Alzheimer Disease Research Center, Ronald M. Loeb Center for Alzheimer's Disease, Icahn School of Medicine at Mount Sinai; Research and Development Service, James J. Peters VA Medical Center, Bronx, New York.

Abstract

Alzheimer's disease (AD) has complex etiologies, and the impact of sex on AD varies over the course of disease development. The literature provides some evidence of sex-specific contributions to AD. However, molecular mechanisms of sex-biased differences in AD remain elusive. Multiomics data in tandem with systems biology approaches offer a new avenue to dissect sex-stratified molecular mechanisms of AD and to develop sex-specific diagnostic and therapeutic strategies for AD. Single-cell transcriptomic datasets and cell deconvolution of bulk tissue transcriptomic data provide additional insights into brain cell type–specific impact on sex-biased differences in AD. In this review, we summarize the impact of sex chromosomes and sex hormones on AD, the impact of sex-biased differences during AD development, and the interplay between sex and a major AD genetic risk factor, the *APOE* ε4 genotype, through the multiomics landscape. Several sex-biased molecular pathways such as neuroinflammation and bioenergetic metabolism have been identified. The importance of sex chromosome and sex hormones, as well as the associated pathways in AD pathogenesis, is further strengthened by findings from omics studies. Future research efforts should integrate the multiomics data from different brain

Address correspondence to Dongming Cai, M.D., Ph.D., at dongming.cai@mssm.edu, or Bin Zhang, Ph.D., at bin.zhang@mssm.edu.

The authors report no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2021.02.968.

regions and different cell types using systems biology approaches, and leverage the knowledge into a holistic examination of sex differences in AD. Advances in systems biology technologies and increasingly available large-scale multiomics datasets will facilitate future studies dissecting such complex signaling mechanisms to better understand AD pathogenesis in both sexes, with the ultimate goals of developing efficacious sex- and *APOE*-stratified preventive and therapeutic interventions for AD.

Alzheimer's disease (AD) is a multifactorial disorder with heterogeneous etiologies. Evidence from basic and clinical studies support sex-specific differences contributing to its complexity. Approximately two-thirds of patients with AD are female (1). Higher AD prevalence in females could be secondary to longer life expectancy or higher dementia incidence in females than in males. Literature reports regarding AD incidents among males and females are conflicting, with some suggesting no differences (2). On the other hand, sex differences in AD have been observed in clinical, neuroimaging, and pathology studies (Supplement). Surprisingly, sex-specific analyses were only performed occasionally during AD clinical trial phases, and the importance of considering sex as a critical modulator of patient responses to treatments was vastly underappreciated (3-6). While it is critical to take into consideration the sex differences in clinical trial design, current challenges reside in the limited knowledge of molecular mechanisms underlying sex-biased differences in AD.

Several mechanisms have been proposed for sex-biased differences in AD, including physiological differences during development, and sex-specific changes during aging and AD development. In recent years, large-scale omics analysis in tandem with systems biology studies has improved our understanding of molecular mechanisms of AD stratified by sex. Multiomics analysis of human AD samples, AD mouse models, and human brain cells derived from inducible pluripotent stem cells of subjects with AD allows researchers to systematically unmask the complexity of sex-mixed samples and reveal sex-biased genomic, genetic, and epigenetic landscapes in AD. Unlike traditional hypothesis-driven studies, multiomics studies enable discovery of novel molecular changes, pathways, and targets common or specific to each sex group in AD development and progression. More importantly, recent advances in single-cell omics studies facilitate in-depth dissection of cell type–specific contributions to disease mechanisms.

While several aspects of sex differences in AD have been discussed extensively in the literature (7-11), we will discuss current studies of sex chromosomes and sex hormones, multiomics analyses of sex-biased differences in AD, and the molecular architecture underlying the interplay between sex and genetic risk factors of AD.

IMPACT OF SEX CHROMOSOMES IN AD

Mounting evidence has suggested that sex chromosomes contribute to the heterogeneity in AD. For example, the molecular cytogenetic analysis showed that somatically acquired X chromosome aneuploidy may contribute to brain aging and neurodegenerative processes. The frequency of X chromosome loss is over 100 times higher in older women (>65 years of age) than in younger women (<16 years of age) (12). The rates of X chromosome aneuploidy were increased twofold in neural cells of the hippocampus and cerebrum

of subjects with AD (13). Furthermore, premature centromere division (PCD), a genetic mechanism associated with increased aneuploidy, is found to be tightly correlated with aging and AD. The average frequency of PCD on the X chromosome in frontal cortical neurons of patients with AD is almost three times higher than that of control subjects (14). Significantly higher percentages of PCD were observed on chromosomes of peripheral lymphocytes of both men and women of advanced age (15) and on the X chromosome of patients with AD (16).

On the other hand, an extra X chromosome may account for protective effects against AD, probably by augmenting the expression of genes that elude X inactivation. Approximately 15% of X-linked genes escape this inactivation, resulting in an increased expression of X-linked genes in females compared with males (17). For example, the loss-of-function mutations in *KDM6A*, a gene encoding a histone demethylase (18), are associated with intellectual disability in humans (19), while deletion of *KDM6A* in $CD4^1$ T cells ameliorated clinical disease and reduced neuropathology in autoimmune disorders like multiple sclerosis, indicating the cell type–specific roles of *KDM6A* in human diseases (20). Consistently, a recent mouse study showed that adding a second X chromosome to hAPP mice confers resilience to AD-related vulnerability in mice, probably through elevating KDM6A expression (21), and that $Kdm6a^{-/-}$ mice manifested synaptic plasticity and memory deficits (22).

Another example of X-inactivation escapees associated with sex differences in developing AD is *PCDH11X*, a gene involved in cell-cell recognition essential for central nervous system function (23,24). It was suggested that *PCDH11X* escapes X inactivation through epigenetic mechanisms (23). A study investigated 2356 patients with AD and 2384 control subjects and found a single nucleotide polymorphism (rs5984894) in the *PCDH11X* gene associated with higher risks of developing AD in women (25). However, two subsequent genome-wide association studies failed to confirm the association between *PCDH11X* polymorphisms and AD (26,27). Moreover, many genes involved in immune processes are located on the X chromosome (28). Compared with males, females demonstrate higher diversity in immune responses due to random inactivation of one of the two X chromosomes and incomplete X inactivation (29). Future studies are needed to understand the regulation of neuroinflammation by X chromosomes.

Furthermore, loss of chromosome Y (LOY) is the most commonly acquired mutation in aging men (30). Dumanski *et al.* (31) investigated the susceptibility to AD in men with LOY in over 3000 subjects. It was found that male subjects with AD had higher degrees of LOY mosaicism, and men with higher levels of LOY had a greater risk of developing AD. It was speculated that LOY might lead to dysregulated immune system function contributing to AD pathogenesis. Moreover, a study of human inducible pluripotent stem cell–derived neurons from a patient with familial AD with presenilin 1 E280A mutation demonstrated that LOY in these neurons exacerbated toxic effects of $A\beta_{42}$ leading to impaired neuronal differentiation and premature cell death (32). Consistently, a recent study of five transcriptomic datasets examined the degrees of extreme downregulation of chromosome Y and observed a significant interaction between age and extreme

downregulation of chromosome Y associated with AD, supporting the role of extreme downregulation of chromosome Y in age-related increased risks of AD in men (33).

Taken together, these lines of studies support the importance of sex chromosomes in contributing to sex-specific vulnerabilities and/or resilience in brain aging and neurodegenerative processes. The long-overlooked roles of sex chromosomes and linked genes in AD pathogenesis may indicate new directions of future studies to understand molecular mechanisms of sex differences in AD.

IMPACT OF SEX HORMONES IN AD

The roles of sex hormones in brain development as well as in aging and AD processes have been well recognized (34-37). Evidence from animal and human studies support functional roles of sex hormones such as estrogens, progesterone, and androgens in cognition and behavior (34,38). With many neuroprotective effects implicated, age-related decreases in sex hormone levels were associated with increased risks of cognitive decline and AD (34,37). For example, reduced exposure to estrogens across the lifetime is associated with increased risks of developing AD in females, whereas age-related decline in both peripheral and brain testosterone levels is associated with increased vulnerabilities of developing AD in males (36). Moreover, changes in sex hormone receptors and downstream signaling pathways during aging have been reported (37). For example, the expression of nonfunctional splicing variants of estrogen receptor alpha in the hippocampus was increased during aging and AD (39), with higher expression levels in female elderly subjects than in males (40,41). In addition, studies identified polymorphisms of estrogen receptors associated with cognitive decline (42) and AD development in females, particularly in *APOE* ε4 (*APOE4*) carriers (43). These data suggest decreased brain responsiveness to sex hormones during aging and AD development.

On the other hand, clinical trial results of sex hormone therapy in AD are rather controversial (34,44-50). Despite earlier studies implicating protective effects of estrogen replacement against AD in females, large clinical studies failed to demonstrate any beneficial effects (51). It was proposed that initiation of hormone replacement in the critical window of perimenopause may lessen the risks of dementia, whereas it may elevate the risks if initiated years after menopause (52). Besides treatment timing, decreased responsiveness at brain receptors and downstream signaling pathways may contribute to the ineffectiveness of hormone therapy. Together, these studies suggest the complexity of sex hormones' involvement in AD.

BULK TISSUE OMICS STUDIES OF SEX DIFFERENCES IN AD

Large-scale bulk tissue omics studies in the recent years have advanced our knowledge of the molecular architecture of sex differences in AD. As shown in Figure 1, we searched published studies of sex differences in AD on PubMed and selected 134 publications for further analysis. Among them, gene association, gene expression, and protein expression studies account for the majority of selected studies showing female-specific changes at molecular levels in the brain, blood, or cerebrospinal fluid (CSF) samples, with only about

20% of studies demonstrating male-specific changes. The reviewed and discussed omics studies in the following section are summarized in Table 1.

Transcriptome-wide sex differences in AD have been characterized in multiple studies. A recent study of 1053 postmortem brain samples across 19 brain regions constructed sex-specific gene coexpression networks for each brain region and found three regions with the most prominent differences between females and males in terms of network topology: the superior parietal lobule, dorsolateral prefrontal cortex, and occipital visual cortex. There were very few commonly shared differentially expressed genes (DEGs) (AD vs. control), except sex hormone genes such as estrogen-related receptor beta differentially expressed in four brain regions (53). A meta-analysis study of protein-protein interaction network revealed important roles for sex steroids in hippocampal neuronal degeneration with androgen and estrogen receptors identified as key drivers of disrupted homeostatic processes of AD neurons (54). The identification of sex hormones through omics studies further strengthens their importance in sex-biased differences in AD. Future studies with multiomics analyses will facilitate a better understanding of the effects of sex hormones and associated pathways on sex-biased vulnerability and treatment responsiveness in AD.

Besides sex hormones, many female-specific pathways have been identified as contributing to AD susceptibilities. A cross-tissue meta-analysis revealed a female-specific immune signature in both brain and blood (55). With network-based analysis and cell type deconvolution approaches, this study analyzed gene expression profiles derived from brain samples of 1084 patients with AD and age-matched control subjects, and whole blood samples of 645 patients with AD and control subjects. More DEGs and gene coexpression modules were identified in women than in men. Many upregulated DEGs in females were enriched in innate and adaptive immune systems, whereas downregulated DEGs were enriched in neurological signaling pathways such as synaptic vehicle exocytosis and autophagy. The blood sample analysis discovered female-specific immune cell-type changes in AD, i.e., increases in neutrophils and naïve B cells and decreases in M2 macrophages, memory B cells, and $CD8^+$ T cells. This study also showed that machine learning predictive models performed better with female-only data, suggesting that molecular changes in females might better model AD-related changes than might those in males. Another meta-analysis examined gene expression changes in AD with eight publicly available microarray datasets from 2088 brain and blood samples and identified a female-specific increase of CXCR4 in AD samples compared with control samples (56). CXCR4 is a chemokine receptor involved in inflammatory signaling pathways, the dysregulation of which is associated with neurodegenerative diseases (57). Female-specific neuroinflammation in AD was also embodied in the female-specific expression pattern of chitinase-3-like 1, a protein related to inflammatory processes and neurodegeneration (58).

Female-biased changes in AD have also been observed in many other pathways associated with the development of amyloid and tau pathology. A genome-wide association study of 1527 male and 1509 female brain and CSF samples from the Religious Orders Study and Rush Memory and Aging Project (ROSMAP) cohort identified a strong association of serpin family B members *SERPINB1, SERPINB6*, and *SERPINB9* with amyloidosis, and *OSTN* and *CLDN16* with tau pathology in females but not in males (59). A transcriptome-wide

meta-analysis of cerebral cortex samples discovered two female-specific AD risk genes associated with tau phosphorylation processes (60), *NCL* and *KIF2A*. Their expression levels were upregulated in females with AD when compared with control females but downregulated in males with AD in contrast to control males. Other female-specific genetic associations in AD such as neurotrophin signaling pathway and polymorphisms in *SERPINB1* have been observed (59,61,62). A meta-analysis of 657 patients with AD and 525 control subjects in a Japanese population identified a significant allelic association between Val66Met of the brain-derived neurotrophic factor gene (*BDNF*) and AD in women (63). A follow-up study of 4711 patients with AD and 4537 control subjects from 16 research centers around the world further confirmed the sex differences in *BDNF* allelic association with the Met66 allele conferring female-specific AD susceptibility.

Consistently, many female-biased changes in AD human studies as described above have been recapitulated in animal studies. A mouse study shows that expression changes of inflammatory mediators (5xFAD vs. control) in the brain were more robust in females than males, with significant expression changes of cytokines (interleukin 1β, interleukin 6) and chemokines (CCL2 and CXCL10) only observed in female brains when compared with control brains (64). Moreover, a study of corticotropin-releasing factor overexpression mice using phosphoproteomic approaches found that cortical phosphopeptides of female corticotropin-releasing factor overexpression mice were overrepresented in tau pathology–related signaling pathways, suggesting a sex-biased corticotropin-releasing factor signaling in tau phosphorylation of AD (65). A mouse study of brain aging also revealed an overall decreased bioenergetic metabolism during early disease transition in female brains, suggesting hypometabolic phenotypes at the onset of AD (66).

Interestingly, some male-specific risk genes are associated with AD, such as *GRN, TREM2*, and *IGF-2* (67-69). For example, a Finnish study of 512 patients with AD and 649 control subjects identified male-specific single nucleotide polymorphisms of *GRN* associated with AD (69). Moreover, in a small cohort of 60 participants, CSF IGF-2 and IGFBP-2 levels were found higher in males with AD when compared with levels of mild cognitive impairment and/or control male counterparts, with no differences seen between groups of female subjects (67). A significant correlation of CSF IGF-2 levels with CSF phosphorylated tau and total tau levels was identified in male subjects as well (67). In addition, significantly higher levels of soluble TREM2 in CSF have been reported in subjects with AD and subjects with frontotemporal dementia than those in normal aging control subjects in a cohort of 180 samples (68). Intriguingly, levels of CSF soluble TREM2 were higher in male than in female participants, suggesting a possibility of sex-biased effects of TREM2 on microglial activation and neurodegeneration in AD (68).

Evidence also indicates the impact of sex on epigenomic signatures of AD (70,71). For example, Mano *et al.* (72) showed hypomethylated CpG islands in the promoter region of a gene aurora kinase C in male subjects with AD, particularly in *APOE4* carriers, but the same CpG islands were hypermethylated in female subjects with AD. In addition, studies demonstrated reduced histone deacetylase 2 levels in female subjects with normal aging, female subjects with mild cognitive impairment, and female subjects with AD when

compared with their male counterparts (73). Moreover, the expression of long noncoding RNAs was found to be different between male and female subjects with AD (74).

While most current studies focus on one or two modalities of omics analysis, little effort was devoted to integrating these studies into a holistic examination at multiscale levels, partially owing to limited data availability as well as technical challenges in developing more integrative systems biology approaches. With increasingly available large-scale omics data and fast-paced advances in integrative multiomics approaches, we will gain more mechanistic insights into AD pathogenesis and sex-biased differences in AD, which will guide future development of sex-stratified preventive and therapeutic interventions.

SINGLE-CELL OMICS STUDIES OF CELL TYPE–SPECIFIC CONTRIBUTIONS TO SEX DIFFERENCES IN AD

It has been increasingly recognized that the complexity of AD pathogenesis may reside in the heterogeneity of disease-associated changes in different brain cell types. While bulk tissue multiomics profiling highlights downregulation of neuronal activities and upregulation of immune responses in AD, the single-cell RNA sequencing enables in-depth dissection of cell type–specific contributions to disease mechanisms during AD development and progression.

A recent seminal study by Mathys *et al.* (75) performed a single-nucleus transcriptomic analysis of the prefrontal cortex of 48 subjects with AD of the ROSMAP (Religious Orders Study and Rush Memory and Aging Project) cohort. It was found that DEGs in neurons were downregulated, whereas most DEGs in non-neuronal cells were upregulated. Cell type–specific DEGs were mostly seen in early AD stages, whereas upregulated DEGs in late AD stage were commonly shared across cell types. More importantly, robust sex-specific differences in association with AD were identified among female and male brain cells. It was demonstrated that AD pathology–associated cell subpopulations were enriched in female cells with higher levels of marker gene expression, whereas no-pathology subpopulations were enriched in male cells. The most dramatic differences in sex-specific transcriptional responses were observed in neurons and oligodendrocytes, with global transcriptional activation in male oligodendrocytes and global downregulation of gene activities in female excitatory and inhibitory neurons that were associated with increased AD pathology, respectively (75). This study provides evidence of sex-dimorphic changes in AD, suggesting greater transcriptional dysregulation accounting for higher disease burden in female subjects with AD.

The importance of microglia in sex-biased differences in AD has also been increasingly recognized. Understanding sex differences in microglial responses to disease states may help unveil sex-biased AD susceptibility. It is well known that the X chromosome contains the largest numbers of immune-related genes and micro-RNAs involved in immune regulation (76-78). In addition, microglia express steroid hormone receptors that are important in microglial sexual differentiation. Once differentiated, microglia maintain transcriptional profiles even in the absence of hormones during adulthood (79). Hormone depletion in

female aging brains led to profound transcriptomic changes with heightened inflammatory responses (80,81), which may contribute to sex differences in developing AD.

A recent study performed transcriptomic and proteomic analyses of microglia from five different brain regions of male and female C57BL/6J mice (82). The baseline phagocytosis was similar, but the expression of major histocompatibility class I and II genes was higher in male cortical microglia than in females, suggesting a higher antigen-presenting capacity. More pronounced differences were seen in the hippocampus, with 1109 DEGs identified between male and female microglia, with only 55 DEGs in cortical microglia. The proteomic analysis indicated that proteins highly expressed in male microglia were involved in toll-like receptor pathways (immune responses after challenges), whereas proteins highly expressed in female microglia were involved in interferon-related processes (82). Another study of transcriptomic profiles of purified male and female hippocampal microglia from embryonic day 18 to postnatal day 60 mice reported that the increases of microglial genes occurred later in males than females, and that microglial maturation accelerated by acute immune stimuli were observed only in males (83).

A study of an AD mouse model identified a stepwise microglia activation with downregulation of microglia checkpoints followed by TREM2-dependent activation (84). However, how sex and *APOE* genotype impact these processes remains to be elucidated. A recent study examined microglial interaction with amyloid plaques in EFAD mouse models and reported significantly lower microglial coverage of amyloid plaques in female mouse brains with the *APOE4* genotype (85). The microglial expression of TREM2 around amyloid plaques was also significantly reduced by *APOE4* genotype and female sex. These studies support the regulatory roles of *APOE* and sex in a TREM2-dependent microglial activation (85).

Furthermore, a study of a microRNA (miRNA) sequencing dataset of microglia identified a unique role of microglial miRNAs in mediating sex-specific responses to tau pathology (86). Using microglia-specific knockout mice of Dicer with the depletion of the miRNA-processing enzyme and Dicer-dependent miRNAs, it was reported that the loss of mature miRNAs led to more dramatic changes in the male microglial transcriptome than in female counterparts with DEGs enriched in immune system pathways suggestive of a heightened inflammatory state. The studies of miRNA and messenger RNA profiles of male and female PS19 mouse models further noted greater changes induced by tau pathology in male microglia than female cells. The male microglia were enriched with genes involved in immune modulation and phagocytosis, characteristic of disease-associated microglia signature, whereas female microglia were enriched with homeostatic microglial genes and human AD genes (86). This study suggests that loss of miRNAs led to sex-dimorphic changes in microglial transcriptome and tauopathy-related phenotypes.

While single-cell or single-nucleus omics studies enable investigations of cell type–specific contributions to AD, future efforts are needed to integrate single-cell and bulk tissue omics data to better understand sex differences in AD and to determine the interactions among different brain cell types during AD development and progression.

THE INTERPLAY OF SEX AND GENETIC RISK FACTORS IN AD

Stratifying genetic association analysis by sex enables the identification of novel AD genetic risk loci and the determination of sex-dependent polygenic risks (87). For example, *BIN1* and *MS4A6A* were found to contribute to AD progression significantly more in females than in males (88). Among many genetic loci that manifest sex-specific effects on AD, the interplay between sex and the *APOE* allele in AD has been extensively explored (89,90). However, only limited multiomics studies have been performed to understand the interplay between *APOE* and sex in AD.

A small cohort of 100 RNA sequencing data derived from four human brain regions examined *APOE4* genotype–associated gene expression patterns. Many more transcription factors differentially expressed in $APOE4^{+}$ females versus $APOE3^{+}$ females than those in $APOE4^{+}$ males versus $APOE3^{+}$ males, with *PSEN2* expressed highest in the temporal cortex of $APOE4^{+}$ females and *CNTNAP2* in $APOE4^{+}$ males (91). A separate study performed transcriptomic and metabolomic analyses of 16-month-old human *APOE* mice (92). There were more DEGs between sexes identified with the *APOE4* genotype when compared with the *APOE3* genotype. Metabolomic analysis showed elevated circulating acylcarnitine levels in *APOE4* females. The study also demonstrated that sex and *APOE* genotype in combination modulate metabolism, bioenergetics, and neuroinflammation processes, and *APOE4* females present with robust gene expression involved in lipid metabolism, antigen presentation, and interferon response genes (92). These observations need to be validated in human samples.

Interestingly, a hypothetic framework proposed by Dumitrescu *et al.* (93) suggests that during the development and progression of AD, genetic regulators of amyloid processes may be largely shared in both sexes, but among amyloid-positive subjects, a sex-specific genetic architecture may emerge with substantial *APOE* contributions to AD in females, including the sex-biased association between *APOE* and tau (94,95). This hypothesis needs to be further tested.

SUMMARY

To better understand the molecular and cellular mechanisms underlying sex-biased differences in AD, multiomics data have been made publicly available and systems biology approaches have been employed to model disease processes. Advances in single-cell and single-nucleus transcriptomic studies enable a better understanding of cell type–specific impact on sex-biased differences in AD. In this review, we discussed current studies of sex chromosomes and sex hormones, as well as multiomics analyses of sex-biased differences in AD processes. It should be noted that to better understand the varying susceptibilities of AD between males and females, it is important to examine sex-biased neurological changes in gene expression profiles and underlying molecular pathways during development and aging (Supplement). Leveraging the knowledge from these processes enables a better understanding of sex-biased differences in neurodegenerative processes.

Several sex-biased signatures in AD have been identified through omics studies, e.g., genes and pathways involved in neuroinflammation and bioenergetic metabolism. The importance of genes and pathways associated with sex chromosomes and sex hormones in AD have been further strengthened by omics studies. The major limitations are that most current analyses focused on one or two modalities of omics data, with little effort devoted to integrating multiomics and multiple studies into a holistic picture of AD. While single-cell or single-nucleus omics studies facilitate in-depth understanding of cell type–specific contributions to AD, future efforts are needed to integrate single-cell and bulk tissue omics data to better understand sex differences in AD and to determine the interactions among different brain cell types during AD development. More importantly, there are many overlooked aspects in studying sex-biased differences in AD such as the roles of sex chromosomes, and the intrinsic differences in male and female brains during development and aging. As summarized in Figure 2, future research should integrate the multiomics data from different brain regions and different cell types into multiscale network analysis and leverage the knowledge from holistic models of sex-biased differences in development and adulthood, aging, and AD. Advances in systems biology technologies and increasingly available large-scale multiomics data will facilitate future studies' dissecting such complex signaling mechanisms to better understand AD pathogenesis in both sexes, with the ultimate goals of developing efficacious sex- and *APOE*-stratified preventive and therapeutic interventions for AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported in part by funding from the National Institutes of Health (Grant Nos. 1R01AG048923 [to DC], RF1AG054014 [to DC and BZ], RO1AG068030 [to DC and BZ], R56AG058655 [to DC and BZ], UO1AG046170 [to BZ], RF1AG057440 [to BZ], RO1AG057907 [to BZ], and UO1AG052411 [to BZ]); and the Department of Veteran Affairs Biomedical Laboratory Research and Development (Grant No. I01BX003380) [to DC], and Rehabilitation Research and Development (Grant No. I01RX002290 [to DC]).

REFERENCES

1. Alzheimer's Association (2020): 2020 Alzheimer's disease facts and figures. Alzheimers Dement 16:391–460.
2. Barnes LL, Wilson RS, Schneider JA, Bienias JL, Evans DA, Bennett DA (2003): Gender, cognitive decline, and risk of AD in older persons. Neurology 60:1777–1781. [PubMed: 12796530]
3. Henley DB, May PC, Dean RA, Siemers ER (2009): Development of semagacestat (LY450139), a functional gamma-secretase inhibitor, for the treatment of Alzheimer's disease. Expert Opin Pharmacother 10:1657–1664. [PubMed: 19527190]
4. Doody RS, Raman R, Farlow M, Iwatsubo T, Vellas B, Joffe S, et al. (2013): A phase 3 trial of semagacestat for treatment of Alzheimer's disease. N Engl J Med 369:341–350. [PubMed: 23883379]
5. Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Kieburtz K, et al. (2014): Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med 370:311–321. [PubMed: 24450890]

6. Farlow M, Arnold SE, van Dyck CH, Aisen PS, Snider BJ, Porsteinsson AP, et al. (2012): Safety and biomarker effects of solanezumab in patients with Alzheimer's disease. Alzheimers Dement 8:261–271. [PubMed: 22672770]
7. Cavedo E, Chiesa PA, Houot M, Ferretti MT, Grothe MJ, Teipel SJ, et al. (2018): Sex differences in functional and molecular neuroimaging biomarkers of Alzheimer's disease in cognitively normal older adults with subjective memory complaints. Alzheimers Dement 14:1204–1215. [PubMed: 30201102]
8. Ferretti MT, Iulita MF, Cavedo E, Chiesa PA, Schumacher Dimech A, Santuccione Chadha A, et al. (2018): Sex differences in Alzheimer disease - the gateway to precision medicine. Nat Rev Neurol 14:457–469. [PubMed: 29985474]
9. Mielke MM, Vemuri P, Rocca WA (2014): Clinical epidemiology of Alzheimer's disease: Assessing sex and gender differences. Clin Epidemiol 6:37–48. [PubMed: 24470773]
10. Nebel RA, Aggarwal NT, Barnes LL, Gallagher A, Goldstein JM, Kantarci K, et al. (2018): Understanding the impact of sex and gender in Alzheimer's disease: A call to action. Alzheimers Dement 14:1171–1183. [PubMed: 29907423]
11. Toro CA, Zhang L, Cao J, Cai D (2019): Sex differences in Alzheimer's disease: Understanding the molecular impact. Brain Res 1719:194–207. [PubMed: 31129153]
12. Russell LM, Strike P, Browne CE, Jacobs PA (2007): X chromosome loss and ageing. Cytogenet Genome Res 116:181–185. [PubMed: 17317957]
13. Yurov YB, Vorsanova SG, Liehr T, Kolotii AD, Iourov IY (2014): X chromosome aneuploidy in the Alzheimer's disease brain. Mol Cytogenet 7:20. [PubMed: 24602248]
14. Spremo-Potparević B, Živković L, Djelić N, Plećaš-Solarović B, Smith MA, Bajić V (2008): Premature centromere division of the X chromosome in neurons in Alzheimer's disease. J Neurochem 106:2218–2223. [PubMed: 18624923]
15. Wojda A, Zietkiewicz E, Mossakowska M, Pawłowski W, Skrzypczak K, Witt M (2006): Correlation between the level of cytogenetic aberrations in cultured human lymphocytes and the age and gender of donors. J Gerontol A Biol Sci Med Sci 61:763–772. [PubMed: 16912092]
16. Spremo-Potparevic B, Zivkovic L, Djelic N, Bajic V (2004): Analysis of premature centromere division (PCD) of the X chromosome in Alzheimer patients through the cell cycle. Exp Gerontol 39:849–854. [PubMed: 15130680]
17. Carrel L, Willard HF (2005): X-inactivation profile reveals extensive variability in X-linked gene expression in females. Nature 434:400–404. [PubMed: 15772666]
18. Greenfield A, Carrel L, Pennisi D, Philippe C, Quaderi N, Siggers P, et al. (1998): The UTX gene escapes X inactivation in mice and humans. Hum Mol Genet 7:737–742. [PubMed: 9499428]
19. Miyake N, Mizuno S, Okamoto N, Ohashi H, Shiina M, Ogata K, et al. (2013): KDM6A point mutations cause Kabuki syndrome. Hum Mutat 34:108–110. [PubMed: 23076834]
20. Itoh Y, Golden LC, Itoh N, Matsukawa MA, Ren E, Tse V, et al. (2019): The X-linked histone demethylase Kdm6a in CD4+ T lymphocytes modulates autoimmunity. J Clin Invest 129:3852–3863. [PubMed: 31403472]
21. Davis EJ, Broestl L, Abdulai-Saiku S, Worden K, Bonham LW, Miñ-ones-Moyano E, et al. (2020): A second X chromosome contributes to resilience in a mouse model of Alzheimer's disease. Sci Transl Med 12:eaaz5677. [PubMed: 32848093]
22. Tang GB, Zeng YQ, Liu PP, Mi TW, Zhang SF, Dai SK, et al. (2017): The histone H3K27 demethylase UTX regulates synaptic plasticity and cognitive behaviors in mice. Front Mol Neurosci 10:267. [PubMed: 28970783]
23. Lopes AM, Ross N, Close J, Dagnall A, Amorim A, Crow TJ (2006): Inactivation status of PCDH11X: Sexual dimorphisms in gene expression levels in brain. Hum Genet 119:267–275. [PubMed: 16425037]
24. O'Leary NA, Wright MW, Brister JR, Ciufo S, Haddad D, McVeigh R, et al. (2016): Reference sequence (RefSeq) database at NCBI: Current status, taxonomic expansion, and functional annotation. Nucleic Acids Res 44:D733–D745. [PubMed: 26553804]
25. Carrasquillo MM, Zou F, Pankratz VS, Wilcox SL, Ma L, Walker LP, et al. (2009): Genetic variation in PCDH11X is associated with susceptibility to late-onset Alzheimer's disease. Nat Genet 41:192–198. [PubMed: 19136949]

26. Beecham GW, Naj AC, Gilbert JR, Haines JL, Buxbaum JD, Pericak-Vance MA (2010): PCDH11X variation is not associated with late-onset Alzheimer disease susceptibility. Psychiatr Genet 20:321–324. [PubMed: 20523261]
27. Miar A, Alvarez V, Corao AI, Alonso B, Díaz M, Menéndez M, et al. (2011): Lack of association between protocadherin 11-X/Y (PCDH11X and PCDH11Y) polymorphisms and late onset Alzheimer's disease. Brain Res 1383:252–256. [PubMed: 21276771]
28. Libert C, Dejager L, Pinheiro I (2010): The X chromosome in immune functions: When a chromosome makes the difference. Nat Rev Immunol 10:594–604. [PubMed: 20651746]
29. Spolarics Z, Peña G, Qin Y, Donnelly RJ, Livingston DH (2017): Inherent X-linked genetic variability and cellular mosaicism unique to females contribute to sex-related differences in the innate immune response. Front Immunol 8:1455. [PubMed: 29180997]
30. Forsberg LA, Gisselsson D, Dumanski JP (2017): Mosaicism in health and disease – clones picking up speed. Nat Rev Genet 18:128–142. [PubMed: 27941868]
31. Dumanski JP, Lambert J-C, Rasi C, Giedraitis V, Davies H, Grenier-Boley B, et al. (2016): Mosaic loss of chromosome Y in blood is associated with Alzheimer disease. Am J Hum Genet 98:1208–1219. [PubMed: 27231129]
32. Mendivil-Perez M, Velez-Pardo C, Kosik KS, Lopera F, Jimenez-DelRio M (2019): IPSCs-derived nerve-like cells from familial Alzheimer's disease PSEN 1 E280A reveal increased amyloid-beta levels and loss of the Y chromosome. Neurosci Lett 703:111–118. [PubMed: 30904577]
33. Caceres A, Jene A, Esko T, Perez-Jurado LA, Gonzalez JR (2020): Extreme downregulation of chromosome Y and Alzheimer's disease in men. Neurobiol Aging 90:150.e1–150.e4.
34. Gurvich C, Hoy K, Thomas N, Kulkarni J (2018): Sex differences and the influence of sex hormones on cognition through adulthood and the aging process. Brain Sci 8:163.
35. McCarthy MM (2016): Multifaceted origins of sex differences in the brain. Philos Trans R Soc Lond B Biol Sci 371:20150106. [PubMed: 26833829]
36. Pike CJ (2017): Sex and the development of Alzheimer's disease. J Neurosci Res 95:671–680. [PubMed: 27870425]
37. Rahman A, Jackson H, Hristov H, Isaacson RS, Saif N, Shetty T, et al. (2019): Sex and gender driven modifiers of Alzheimer's: The role for estrogenic control across age, race, medical, and lifestyle risks. Front Aging Neurosci 11:315. [PubMed: 31803046]
38. Gurvich C, Thomas N, Kulkarni J (2020): Sex differences in cognition and aging and the influence of sex hormones. Handb Clin Neurol 175:103–115. [PubMed: 33008519]
39. Ishunina TA, Fischer DF, Swaab DF (2007): Estrogen receptor alpha and its splice variants in the hippocampus in aging and Alzheimer's disease. Neurobiol Aging 28:1670–1681. [PubMed: 17010478]
40. Foster TC (2012): Role of estrogen receptor alpha and beta expression and signaling on cognitive function during aging. Hippocampus 22:656–669. [PubMed: 21538657]
41. Rettberg JR, Yao J, Brinton RD (2014): Estrogen: A master regulator of bioenergetic systems in the brain and body. Front Neuroendocrinol 35:8–30. [PubMed: 23994581]
42. Yaffe K, Lindquist K, Sen S, Cauley J, Ferrell R, Penninx B, et al. (2009): Estrogen receptor genotype and risk of cognitive impairment in elders: Findings from the Health ABC study. Neurobiol Aging 30:607–614. [PubMed: 17889406]
43. Ryan J, Carriere I, Carcaillon L, Dartigues JF, Auriacombe S, Rouaud O, et al. (2014): Estrogen receptor polymorphisms and incident dementia: The prospective 3C study. Alzheimers Dement 10:27–35. [PubMed: 23491264]
44. Gleason CE, Dowling NM, Wharton W, Manson JE, Miller VM, Atwood CS, et al. (2015): Effects of hormone therapy on cognition and mood in recently postmenopausal women: Findings from the randomized, controlled KEEPS-Cognitive and Affective Study. PLoS Med 12:e1001833. [PubMed: 26035291]
45. Henderson VW, St John JA, Hodis HN, McCleary CA, Stanczyk FZ, Shoupe D, et al. (2016): Cognitive effects of estradiol after menopause: A randomized trial of the timing hypothesis. Neurology 87:699–708. [PubMed: 27421538]

46. Hodis HN, Mack WJ, Shoupe D, Azen SP, Stanczyk FZ, Hwang-Levine J, et al. (2015): Methods and baseline cardiovascular data from the Early versus Late Intervention Trial with Estradiol testing the menopausal hormone timing hypothesis. Menopause 22:391–401. [PubMed: 25380275]
47. Maki PM (2013): Critical window hypothesis of hormone therapy and cognition: A scientific update on clinical studies. Menopause 20:695–709. [PubMed: 23715379]
48. Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, et al. (2004): Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA 291:2947–2958. [PubMed: 15213206]
49. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al. (2003): Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: The Women's Health Initiative Memory Study: A randomized controlled trial. JAMA 289:2651–2662. [PubMed: 12771112]
50. Zandi PP, Carlson MC, Plassman BL, Welsh-Bohmer KA, Mayer LS, Steffens DC, et al. (2002): Hormone replacement therapy and incidence of Alzheimer disease in older women: The Cache County Study. JAMA 288:2123–2129. [PubMed: 12413371]
51. Barron AM, Pike CJ (2012): Sex hormones, aging, and Alzheimer's disease. Front Biosci (Elite Ed) 4:976–997. [PubMed: 22201929]
52. Whitmer RA, Quesenberry CP, Zhou J, Yaffe K (2011): Timing of hormone therapy and dementia: The critical window theory revisited. Ann Neurol 69:163–169. [PubMed: 21280086]
53. Sun L-L, Yang S-L, Sun H, Li W-D, Duan S-R (2019): Molecular differences in Alzheimer's disease between male and female patients determined by integrative network analysis. J Cell Mol Med 23:47–58. [PubMed: 30394676]
54. Winkler JM, Fox HS (2013): Transcriptome meta-analysis reveals a central role for sex steroids in the degeneration of hippocampal neurons in Alzheimer's disease. BMC Syst Biol 7:51. [PubMed: 23803348]
55. Paranjpe MD, Belonwu S, Wang JK, Oskotsky T, Gupta A, Taubes A, et al. (2021): Sex-specific cross tissue meta-analysis identifies immune dysregulation in women with Alzheimer's disease. Front Aging Neurosci 13:735611. [PubMed: 34658838]
56. Brooks LRK, Mias GI (2019): Data-driven analysis of age, sex, and tissue effects on gene expression variability in Alzheimer's disease. Front Neurosci 13:392–392. [PubMed: 31068785]
57. Bonham LW, Karch CM, Fan CC, Tan C, Geier EG, Wang Y, et al. (2018): CXCR4 involvement in neurodegenerative diseases. Transl Psychiatry 8:73. [PubMed: 29636460]
58. Sanfilippo C, Castrogiovanni P, Imbesi R, Kazakowa M, Musumeci G, Blennow K, et al. (2019): Sex difference in CHI3L1 expression levels in human brain aging and in Alzheimer's disease. Brain Res 1720:146305. [PubMed: 31247206]
59. Deming Y, Dumitrescu L, Barnes LL, Thambisetty M, Kunkle B, Gifford KA, et al. (2018): Sex-specific genetic predictors of Alzheimer's disease biomarkers. Acta Neuropathol 136:857–872. [PubMed: 29967939]
60. Cáceres A, González JR (2020): Female-specific risk of Alzheimer's disease is associated with tau phosphorylation processes: A transcriptome-wide interaction analysis. Neurobiol Aging 96:104–108. [PubMed: 32977080]
61. Aguirre CC, Baudry M (2009): Progesterone reverses 17beta-estradiol-mediated neuroprotection and BDNF induction in cultured hippocampal slices. Eur J Neurosci 29:447–454. [PubMed: 19175406]
62. Fisher DW, Bennett DA, Dong H (2018): Sexual dimorphism in predisposition to Alzheimer's disease. Neurobiol Aging 70:308–324. [PubMed: 29754747]
63. Fukumoto N, Fujii T, Combarros O, Kamboh MI, Tsai SJ, Matsushita S, et al. (2010): Sexually dimorphic effect of the Val66Met polymorphism of BDNF on susceptibility to Alzheimer's disease: New data and meta-analysis. Am J Med Genet B Neuropsychiatr Genet 153B:235–242. [PubMed: 19504537]
64. Manji Z, Rojas A, Wang W, Dingledine R, Varvel NH, Ganesh T (2019): 5xFAD mice display sex-dependent inflammatory gene induction during the prodromal stage of Alzheimer's disease. J Alzheimers Dis 70:1259–1274. [PubMed: 31322556]

65. Bangasser DA, Dong H, Carroll J, Plona Z, Ding H, Rodriguez L, et al. (2017): Corticotropin-releasing factor overexpression gives rise to sex differences in Alzheimer's disease-related signaling. Mol Psychiatry 22:1126–1133. [PubMed: 27752081]
66. Zhao L, Mao Z, Woody SK, Brinton RD (2016): Sex differences in metabolic aging of the brain: Insights into female susceptibility to Alzheimer's disease. Neurobiol Aging 42:69–79. [PubMed: 27143423]
67. Aberg D, Johansson P, Isgaard J, Wallin A, Johansson JO, Andreasson U, et al. (2015): Increased cerebrospinal fluid level of insulin-like growth factor-II in male patients with Alzheimer's disease. J Alzheimers Dis 48:637–646. [PubMed: 26402100]
68. Piccio L, Deming Y, Del-Aguila JL, Ghezzi L, Holtzman DM, Fagan AM, et al. (2016): Cerebrospinal fluid soluble TREM2 is higher in Alzheimer disease and associated with mutation status. Acta Neuropathol 131:925–933. [PubMed: 26754641]
69. Viswanathan J, Makinen P, Helisalmi S, Haapasalo A, Soininen H, Hiltunen M (2009): An association study between granulin gene polymorphisms and Alzheimer's disease in Finnish population. Am J Med Genet B Neuropsychiatr Genet 150B:747–750. [PubMed: 19016491]
70. Boks MP, Derks EM, Weisenberger DJ, Strengman E, Janson E, Sommer IE, et al. (2009): The relationship of DNA methylation with age, gender and genotype in twins and healthy controls. PLoS One 4:e6767. [PubMed: 19774229]
71. El-Maarri O, Becker T, Junen J, Manzoor SS, Diaz-Lacava A, Schwaab R, et al. (2007): Gender specific differences in levels of DNA methylation at selected loci from human total blood: A tendency toward higher methylation levels in males. Hum Genet 122:505–514. [PubMed: 17851693]
72. Mano T, Nagata K, Nonaka T, Tarutani A, Imamura T, Hashimoto T, et al. (2017): Neuron-specific methylome analysis reveals epigenetic regulation and tau-related dysfunction of BRCA1 in Alzheimer's disease. Proc Natl Acad Sci U S A 114:E9645–E9654. [PubMed: 29042514]
73. Mahady L, Nadeem M, Malek-Ahmadi M, Chen K, Perez SE, Mufson EJ (2019): HDAC2 dysregulation in the nucleus basalis of Meynert during the progression of Alzheimer's disease. Neuropathol Appl Neurobiol 45:380–397. [PubMed: 30252960]
74. Cao M, Li H, Zhao J, Cui J, Hu G (2019): Identification of age- and gender-associated long noncoding RNAs in the human brain with Alzheimer's disease. Neurobiol Aging 81:116–126. [PubMed: 31280115]
75. Mathys H, Davila-Velderrain J, Peng Z, Gao F, Mohammadi S, Young JZ, et al. (2019): Single-cell transcriptomic analysis of Alzheimer's disease. Nature 570:332–337. [PubMed: 31042697]
76. Klein SL, Flanagan KL (2016): Sex differences in immune responses. Nat Rev Immunol 16:626–638. [PubMed: 27546235]
77. Pinheiro I, Dejager L, Libert C (2011): X-chromosome-located micro-RNAs in immunity: Might they explain male/female differences? The X chromosome-genomic context may affect X-located miRNAs and downstream signaling, thereby contributing to the enhanced immune response of females. Bioessays 33:791–802. [PubMed: 21953569]
78. Fish EN (2008): The X-files in immunity: Sex-based differences predispose immune responses. Nat Rev Immunol 8:737–744. [PubMed: 18728636]
79. Villa A, Gelosa P, Castiglioni L, Cimino M, Rizzi N, Pepe G, et al. (2018): Sex-specific features of microglia from adult mice. Cell Rep 23:3501–3511. [PubMed: 29924994]
80. Benedusi V, Meda C, Della Torre S, Monteleone G, Vegeto E, Maggi A (2012): A lack of ovarian function increases neuroinflammation in aged mice. Endocrinology 153:2777–2788. [PubMed: 22492304]
81. Sarvari M, Hrabovszky E, Kallo I, Solymosi N, Liko I, Berchtold N, et al. (2012): Menopause leads to elevated expression of macrophage-associated genes in the aging frontal cortex: Rat and human studies identify strikingly similar changes. J Neuroinflammation 9:264. [PubMed: 23206327]
82. Guneykaya D, Ivanov A, Hernandez DP, Haage V, Wojtas B, Meyer N, et al. (2018): Transcriptional and translational differences of microglia from male and female brains. Cell Rep 24:2773–2783.e6. [PubMed: 30184509]

83. Hanamsagar R, Alter MD, Block CS, Sullivan H, Bolton JL, Bilbo SD (2018): Generation of a microglial developmental index in mice and in humans reveals a sex difference in maturation and immune reactivity. Glia 66:460. [PubMed: 29230901]
84. Keren-Shaul H, Spinrad A, Weiner A, Matcovitch-Natan O, Dvir-Szternfeld R, Ulland TK, et al. (2017): A unique microglia type associated with restricting development of Alzheimer's disease. Cell 169:1276–1290.e17. [PubMed: 28602351]
85. Stephen TL, Cacciottolo M, Balu D, Morgan TE, LaDu MJ, Finch CE, et al. (2019): APOE genotype and sex affect microglial interactions with plaques in Alzheimer's disease mice. Acta Neuropathol Commun 7:82. [PubMed: 31113487]
86. Kodama L, Guzman E, Etchegaray JI, Li Y, Sayed FA, Zhou L, et al. (2020): Microglial microRNAs mediate sex-specific responses to tau pathology. Nat Neurosci 23:167–171. [PubMed: 31873194]
87. Gamache J, Yun Y, Chiba-Falek O (2020): Sex-dependent effect of APOE on Alzheimer's disease and other age-related neurodegenerative disorders. Dis Model Mech 13:dmm045211. [PubMed: 32859588]
88. Fan CC, Banks SJ, Thompson WK, Chen CH, McEvoy LK, Tan CH, et al. (2020): Sex-dependent autosomal effects on clinical progression of Alzheimer's disease. Brain 143:2272–2280. [PubMed: 32591829]
89. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. (1997): Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA 278:1349–1356. [PubMed: 9343467]
90. Neu SC, Pa J, Kukull W, Beekly D, Kuzma A, Gangadharan P, et al. (2017): Apolipoprotein E genotype and sex risk factors for Alzheimer disease: A meta-analysis. JAMA Neurol 74:1178–1189. [PubMed: 28846757]
91. Hsu M, Dedhia M, Crusio WE, Delprato A (2019): Sex differences in gene expression patterns associated with the APOE4 allele. F1000Res 8:387. [PubMed: 31448102]
92. Shang Y, Mishra A, Wang T, Wang Y, Desai M, Chen S, et al. (2020): Evidence in support of chromosomal sex influencing plasma based metabolome vs APOE genotype influencing brain metabolome profile in humanized APOE male and female mice. PLoS One 15:e0225392. [PubMed: 31917799]
93. Dumitrescu L, Mayeda ER, Sharman K, Moore AM, Hohman TJ (2019): Sex differences in the genetic architecture of Alzheimer's disease. Curr Genet Med Rep 7:13–21. [PubMed: 31360619]
94. Altmann A, Tian L, Henderson VW, Greicius MD, Alzheimer's Disease Neuroimaging Initiative Investigators (2014): Sex modifies the APOE-related risk of developing Alzheimer disease. Ann Neurol 75:563–573. [PubMed: 24623176]
95. Hohman TJ, Dumitrescu L, Barnes LL, Thambisetty M, Beecham G, Kunkle B, et al. (2018): Sex-specific association of apolipoprotein E with cerebrospinal fluid levels of tau. JAMA Neurol 75:989–998. [PubMed: 29801024]

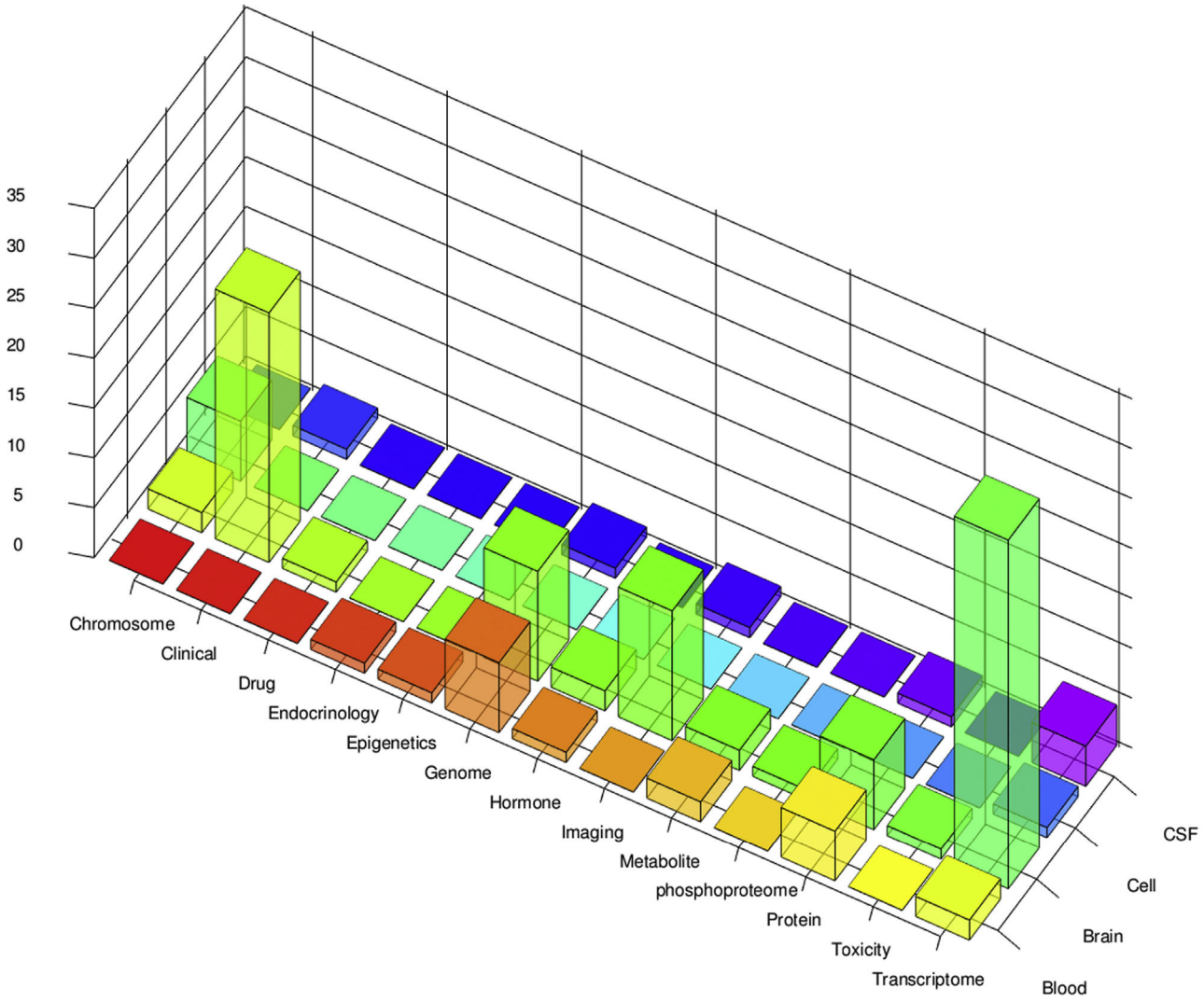

Figure 1.

A summary of multiomics studies published in the literature. To explore the studies focused on sex differences in Alzheimer's disease, we searched on PubMed with the key words *Alzheimer, sex, gender, men, women, male*, and *female*. The search resulted in over 800 publications. We then manually scanned these studies and selected 134 publications covering multiple areas for further analysis. Among them, gene association studies, gene expression studies, and protein expression studies are in the majority (82%) (Table S1). Over 75% of the selected omics studies showed female-specific changes at molecular levels in the brain, blood, or cerebrospinal fluid (CSF), while only about 20% showed male-specific changes.

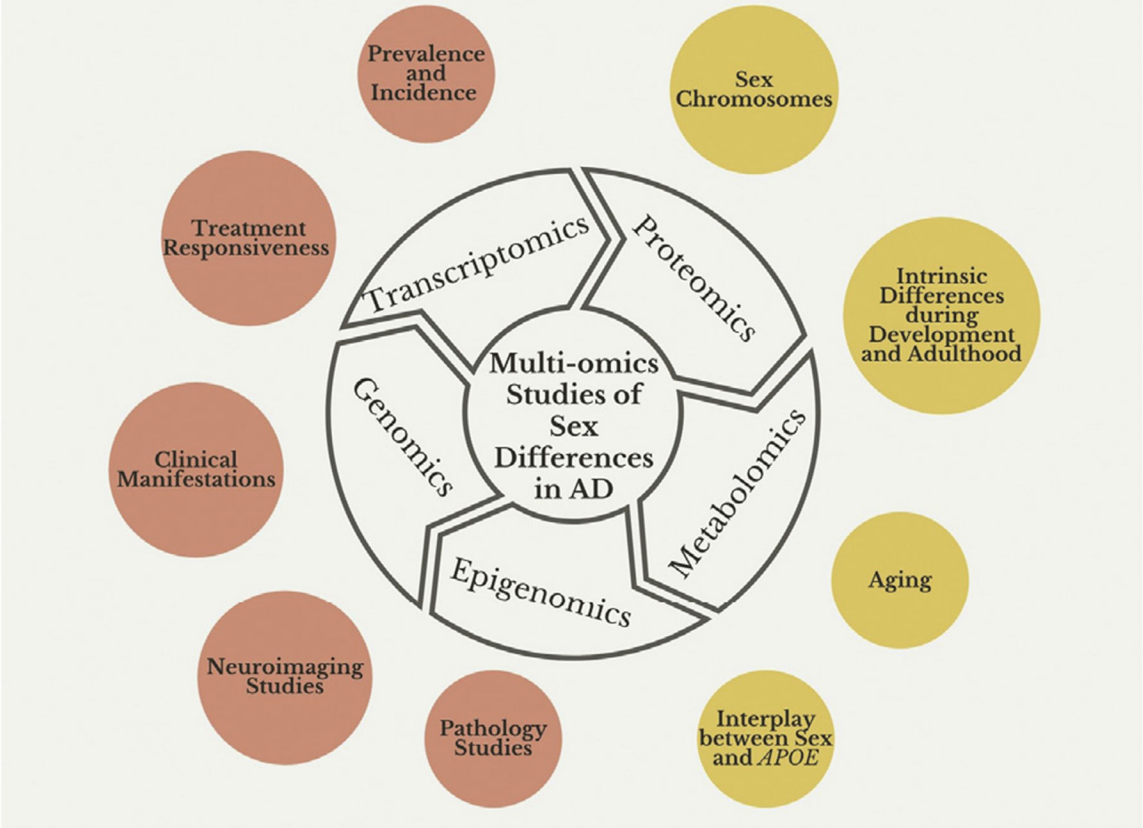

Figure 2.

A holistic overview of sex differences in Alzheimer's disease (AD). Future studies need to take into considerations of different aspects of sex differences in AD including prevalence/incidence, clinical manifestations, neuroimaging studies, and pathology studies as well as treatment responsiveness. The integration of multiomics studies such as transcriptomics, proteomics, metabolomics, epigenomics, and genomics data will facilitate a better understanding of sex differences in AD. More importantly, leveraging the knowledge from studies of sex chromosomes, intrinsic differences in development and adulthood such as sex hormones, aging processes, and the interplay between sex and other genetic rick factors like *APOE* will enable a holistic examination of sex differences in AD, guiding future development of efficacious sex- and *APOE*-stratified preventive and therapeutic interventions for AD.

Table 1.

Detailed Information of Large-Scale Omics Studies Cited, Discussed, or Reviewed in the Article

Study	Year	Organism	Tissue	Experiment	Sample Size	Focus
Impact of Sex Chromosomes in AD						
Yurov *et al.* (13)	2014	Human	Brain	Genetic abnormalities	20	Sex chromosome
Spremo-Potparević *et al.* (14)	2008	Human	Chromosome	Genetic abnormalities	10	Sex chromosome
Wojda *et al.* (15)	2006	Human	Blood	Genetic abnormalities	123	Sex chromosome
Spremo-Potparevic *et al.* (16)	2004	Human	Chromosome	Cytogenetic analysis	23	Sex chromosome
Carrel and Willard (17)	2005	Human	Human cells	Chromosomal expression	40 fibroblast lines with 931 X-linked transcripts	Sex chromosome
Greenfield *et al.* (18)	1998	Human Mice	Brain	Chromosomal expression	Human and mouse cDNA clones	Sex chromosome
Miyake *et al.* (19)	2013	Human	Brain	Genetic variation	32	Genomic (*KDM6A*)
Itoh *et al.* (20)	2019	Mice	Brain	Gene expression	34	Histone demethylase (*KDM6A*)
Davis *et al.* (21)	2020	Human Mice	Chromosome	Chromosomal modification	6065 (human) 10–15 per group (mice)	Sex chromosome
Tang *et al.* (22)	2017	Mice	Brain	Gene expression	70	Histone demethylase
Lopes *et al.* (23)	2006	Human	Brain	Gene expression	58	Gene expression on autism
Carrasquillo *et al.* (25)	2009	Human	Brain	Genetic variation	2099	Genomic (*PCDH11X*)
Beecham *et al.* (26)	2010	Human	Brain	Gene expression	1739	*PCDH11X* gene on AD
Miar *et al.* (27)	2011	Human	Brain	Gene expression	770	SNP and *PCDH11X* on AD
Dumanski *et al.* (31)	2016	Human	Brain	Chromosomal expression	1611	Sex chromosome
Mendevil-Perez *et al.* (32)	2019	Human	Stem cells	Chromosomal modification	2	Sex chromosome
Caceres *et al.* (33)	2020	Human	Brain/blood	Chromosomal expression	1018	Sex chromosome
Impact of Sex Hormones in AD						
Ishunina *et al.* (39)	2007	Human	Hippocampal tissue	Gene expression	27	ER and splicing variants
Yaffe *et al.* (42)	2009	Human	Blood	SNP	1343 females 1184 males	ER polymorphisms
Ryan *et al.* (43)	2014	Human	Blood	SNP	6959	ER polymorphisms *APOE4* association
Gleason *et al.* (44)	2015	Human		Hormone therapy Clinical trial	727	Efficacy
Henderson *et al.* (45)	2016	Human		Hormone therapy Clinical trial	567	Efficacy regarding timing Perimenopausal vs after menopause

Study	Year	Organism	Tissue	Experiment	Sample Size	Focus
Shumaker *et al.* (48)	2004	Human		Hormone therapy Clinical trial	1464 estrogen vs. 1483 placebo; 3693 estrogen + progesterone vs. 3786 placebo	Efficacy
Shumaker *et al.* (49)	2003	Human		Hormone therapy Clinical trial	2229 estrogen + progesterone vs. 2303 placebo	Efficacy
Zandi *et al.* (50)	2002	Human		Prospective clinical studies	1357 men 1889 women	HRT Incidence of AD
Bulk Tissue Omics Studies						
Sun *et al.* (53)	2019	Human	Brain	Transcriptomics	1053 19 brain regions 125 subjects	Sex-biased gene topology in different brain regions
Winkler and Fox (54)	2013	Human	Hippocampal neurons	Transcriptomics	17 AD and 21 control cases	Sex steroid pathways
Paranjpe *et al.* (55)	2020	Human	Brain/blood	Transcriptomics	1084 (brain) 645 (blood)	Female-specific immune signature
Brooks and Mias (56)	2019	Human	Brain/blood	Microarray	2088	Female-specific increase in CXCR4
Sanfilippo *et al.* (58)	2019	Human	Brain	Microarray	992 subjects with AD and 1290 control subjects	Female-specific increase in *CHI3L1*
Deming *et al.* (59)	2018	Human	Brain/CSF	GWAS	3036	Sex-specific GWAS loci in AD
Cáceres and González (60)	2020	Human	Brain	Transcriptomics	785	Sex-biased tau phosphorylation
Fukumoto *et al.* (63)	2010	Human	Tissue	Gene expression	1182	BDNF SNPs
Bangasser *et al.* (65)	2017	Rat	Brain tissue	Protein receptor expression	40	CRF expression on AD
Zhao *et al.* (66)	2016	Mouse	Brain	Targeted array of qPCR of 182 genes	40	Hypometabolism phenotypes in AD
Aberg *et al.* (67)	2015	Human	Brain/CSF	Protein expression	80	Insulin growth factor in CSF AD
Piccio *et al.* (68)	2016	Human	Brain/CSF	Protein expression	107	sTREM2 in AD CSF
Viswanathan *et al.* (69)	2009	Human	Blood	SNPs	1161	*GRN* polymorphisms in AD
Boks *et al.* (70)	2009	Human	Blood	DNA methylation	188	Methylation modified by age and sex
El-Maarri *et al.* (71)	2007	Human	Brain	Epigenomics	192	Sex-biased epigenetics in AD
Mano *et al.* (72)	2017	Human	Brain/tissue	Methylation microarray	60	Epigenetics in tau and AD
Mahady *et al.* (73)	2019	Human	Brain/tissue	Protein, IHC	61	HDAC2 dysregulation in AD brain
Cao *et al.* (74)	2019	Human	Brain	Microarray	214	Long ncRNAs in AD
Single-Cell Omics Studies						
Mathys *et al.* (75)	2019	Human/mice	Cell/tissue	Transcriptomics	48	Brain cell types in AD
Pinheiro *et al.* (77)	2011	Human/mice	Brain	Transcriptomics	48	MicroRNA and X chromosome
Villa *et al.* (79)	2018	Mice	Brain/tissue	Transcriptomics	24	Sex features on microglia in mice

Study	Year	Organism	Tissue	Experiment	Sample Size	Focus
Sarvari *et al.* (81)	2012	Human/rat	Brain	Transcriptomics	39	Menopause and macrophage
Guneykaya *et al.* (82)	2018	Mice	Brain	Transcriptomics	6	Microglia in male female brains
Hanamsagar *et al.* (83)	2018	Mice	Brain	Transcriptomics	20	Microglia on AD sex differences
Keren-Shaul *et al.* (84)	2017	Mice	Brain/tissue	Transcriptomics	12	Microglia in AD
Stephen *et al.* (85)	2019	Mice	Brain/tissue	Transcriptomics	25	Sex and AD with microglia
Kodama L *et al.* (86)	2020	Mice	Brain/tissue	Transcriptomics	87	Sex effect on microglia and AD
The Interplay of Sex and Genetic Risk Factors in AD						
Hsu *et al.* (91)	2019	Human	Brain	Transcription factors	100	*APOE* and conversion of MCI to AD
Shang *et al.* (92)	2020	Mice	Brain/blood	Transcriptomics Metabolomics	40	*APOE* on metabolome

AD, Alzheimer's disease; *APOE4, APOE* ε4; cDNA, complementary DNA; CRF, corticotropin-releasing factor; CSF, cerebrospinal fluid; ER, estrogen receptor; GWAS, genome-wide association study; HRT, hormone replacement therapy; IHC, immunohistochemistry; MCI, mild cognitive impairment; ncRNA, noncoding RNA; qPCR, quantitative polymerase chain reaction; SNP, single nucleotide polymorphism.