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Paul C. Guest *Editor*

Reviews on Biomarker Studies in Psychiatric and Neurodegenerative Disorders

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Preface

Although hundreds of biomarker candidates for psychiatric and neurodegenerative illnesses have been proposed over the last 20 years, only a handful of these have been approved by the regulatory authorities and put into practice in the clinic. This shortfall is most likely due to inconsistencies across laboratories during the early discovery phases and may be a result of factors, such as technical deviations within and across platforms, insufficient validation of candidates, and a widespread lack of awareness across the scientific and medical communities on the essential criteria and regulatory requirements for incorporating biomarkers into the research and drug development pipelines. Success in this area has also been complicated by the reality that psychiatric and neurodegenerative diseases are not homogeneous in nature and can consist of multiple etiologies and subtypes, rendering their complete characterization extremely difficult.

It is now recognized throughout the scientific and medical communities that robust tests incorporating biomarker readouts are urgently needed to improve diagnosis of patients suffering from conditions such as schizophrenia, depression, bipolar disorder, autism spectrum disorders, and Alzheimer's disease. The availability of such tests have many anticipated benefits stemming from the fact that an accurate and early diagnosis will lead to improved outcomes by helping to place patients on the correct treatment at the earliest possible time. This is critical as pathological effects appear to be increasingly ingrained over time. Biomarker tests can also serve as surrogate markers of response to treatment as well as for the risk of developing unwanted side effects. In a similar manner, biomarker-based tests could also be used as surrogate response agents in the development of new and better drugs for treatment of these complex disorders. This would be a significant breakthrough as only a limited number of drug entities have been developed in this arena over the last 20 years, and most of these come at the price of having significant side effects.

This book includes a series of reviews on general aspects of biomarker use in the study of psychiatric and neurodegenerative diseases and the development of novel medications in these areas. The chapters come from international experts in these fields and arise from five continents, including the countries of Brazil, China, Denmark, France, Germany, Italy, Japan, Poland, Spain, the United Kingdom, and

the United States. Each chapter describes the pros and cons of the various approaches and covers the successes and failures in this research field. It is only by a thorough understanding of the shortcomings that progress can be made. The overall goal is to facilitate a better understanding for improved treatment of these disorders by providing a viable mechanism of catching up with other areas of modern medicine, such as diabetes and heart disease. Finally, it is anticipated that the development and application of valid biomarker tests will help the treatment of individuals suffering with these disorders of the mind move into the area of personalized medicine where the right patients can receive the right medication at the right time for the best possible outcome.

Campinas, SP, Brazil Paul C. Guest

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Chapter 1
The Potential of 'Omics to Link Lipid Metabolism and Genetic and Comorbidity Risk Factors of Alzheimer's Disease in African Americans

Kaitlyn E. Stepler and Renã A. S. Robinson

Abstract Alzheimer's disease (AD) disproportionately affects African Americans (AAs) and Hispanics, who are more likely to have AD than non-Hispanic Whites (NHWs) and Asian Americans. Racial disparities in AD are multifactorial, with potential contributing factors including genetics, comorbidities, diet and lifestyle, education, healthcare access, and socioeconomic status. Interestingly, comorbidities such as hypertension, type 2 diabetes mellitus, and cardiovascular disease also impact AAs. It is plausible that a common underlying molecular basis to these higher incidences of AD and comorbidities exists especially among AAs. A likely common molecular pathway that is centrally linked to AD and these noted comorbidities is alterations in lipid metabolism. Several genes associated with AD risk—most notably, the ε4 allele of the apolipoprotein E (APOE) gene and several mutations in the ATP-binding cassette transporter A7 (ABCA7) gene—are linked to altered lipid metabolism, especially in AAs. This review explores the role of lipid metabolism in AD broadly, as well as in other comorbidities that are prevalent in AAs. Because there are gaps in our understanding of the molecular basis of higher incidences of AD in AAs, 'omics approaches such as proteomics and lipidomics are presented as potential methods to improve our knowledge in these areas.

Keywords Lipid metabolism · Alzheimer's disease · Proteomics · African Americans · Comorbidities · Lipidomics

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1.1 Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder marked by accumulation of extracellular amyloid beta (Aβ) plaques and intracellular hyperphosphorylated tau tangles [also referred to as senile plaques and neurofibrillary tangles, (NFTs)] in the brain, which lead to neuronal dysfunction and death. Other primary hallmarks of the disease include mitochondrial dysfunction, decreased synaptic plasticity, compromised blood-brain barrier, and oxidative stress. According to the Alzheimer's Association, approximately 5.7 million Americans have AD [1], although this number is not equally spread among different subgroups of the population. AD disproportionately affects certain racial subgroups, which is alarming considering that underrepresented minorities will comprise a larger proportion of both the entire older population and the population of AD sufferers by 2050 [2–4]. AD and related dementia prevalence are both higher in African Americans (AAs) and Hispanics than in non-Hispanic Whites (NHWs) and Asian Americans [3, 5–7]. In terms of incidence, AAs are 2–3 and Hispanics are about 1.5 times as likely to develop AD and related dementias compared to NHWs [8, 9], and AAs have a 65% higher risk than Asian Americans [10]. AAs and Hispanics also have a higher prevalence of cognitive impairment in adults aged 55 and older compared to NHWs [3].

Although it is well-established that racial disparities exist in AD, there are many contributing factors such as socioeconomic aspects, genetics, and comorbidities, and whether or not there are molecular underpinnings related to these remains unknown. Socioeconomic factors include education level, healthcare access, and willingness to seek care and treatment which are noted in AD as having differences between racial subgroups [7, 9]. AAs are less likely than NHWs to seek care for symptoms of mild cognitive impairment (MCI), a preliminary stage of AD [11], and are less likely than NHWs to receive AD pharmacotherapy treatment (e.g., cholinesterase inhibitors or memantine) upon disease diagnosis [2, 12]. Prevalence of genetic risk factors such as the ε4 allele of the apolipoprotein E (APOE) gene and various single-nucleotide polymorphisms (SNPs) in the ATP-binding cassette transporter A7 (ABCA7) gene and comorbidities, such as cardiovascular disease and type 2 diabetes mellitus (T2DM) that increase risk of AD, also contribute to racial disparities in AD. Prevalence of comorbidities is suggested to be a larger contributing factor than genetics [8].

One common molecular pathway that affects both genetic and comorbidity factors in AD is alterations in lipid metabolism. Significant evidence links dysregulation of lipid metabolism to AD [13–15]. Lipids play an integral role in AD pathogenesis through their interaction with Aβ, particularly in cell membranes and lipid rafts that can promote Aβ aggregation and disrupt membrane integrity (Fig. 1.1) [16]. Lipid rafts can affect amyloid precursor protein (APP) processing leading to an increase in Aβ production [16, 17]. Impaired cholesterol metabolism has been implicated in tau hyperphosphorylation processes and leads to increased oxidative stress, inflammation, phospholipase activation, and vascular dysfunction (Fig. 1.1) [16, 18]. Lipids contribute to neuronal dysfunction and dystrophy, disruption of the autophagy/lysosomal system, increased apoptosis, and compromised membrane function [19, 20].

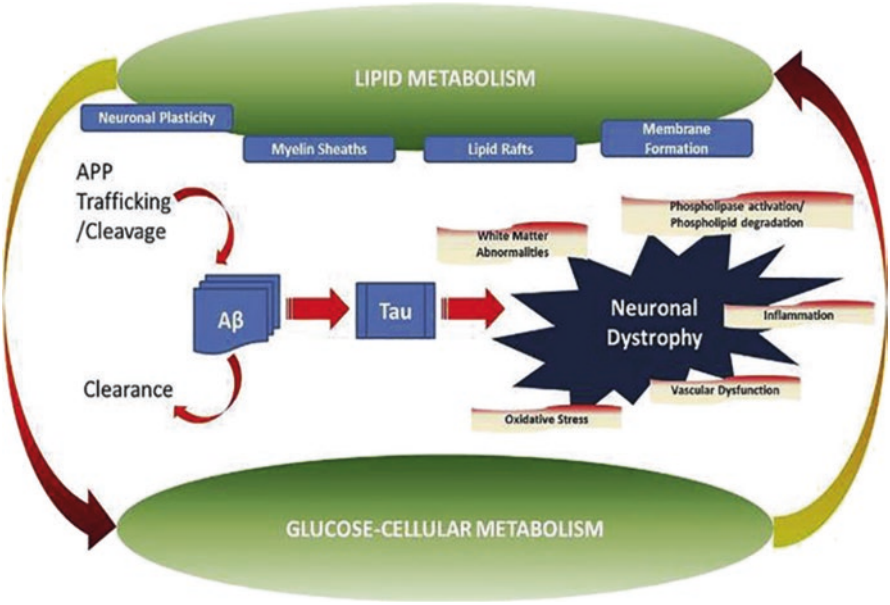

Fig. 1.1 Relationship of glucose-cellular metabolism and lipid metabolism in AD pathogenesis (source: see Ref. [20])

It is clear that lipid metabolism is important in AD pathogenesis and, as we will describe in this review, especially important in comorbidities affecting AAs. Mechanisms of lipid metabolism in AD are not fully understood, and their role in racial disparities of AD is unexplored. Fortunately, 'omics approaches are powerful methods with which to study molecules in lipid metabolism pathways in this context. 'Omics approaches, which include genomics, proteomics, metabolomics, and lipidomics, allow thousands of molecules to be investigated simultaneously and can give a systematic insight to changes in lipid metabolism in tissues. Such insight is important to help with tailored AD prevention, early diagnosis, and personalized treatment strategies for racial groups with high incidences of AD.

1.2 Potential Roles of Lipid Metabolism in AD Racial Disparities

The differences in AD prevalence and incidence among AAs and NHWs noted above are significant and can be partially evaluated by disease presentation and cognitive performance. AAs and Hispanics are more likely to present with more severe symptoms than NHWs [2, 9], and AAs are more likely to present at an earlier age of onset than NHWs [2]. Several studies demonstrate that AAs tend to score lower on cognitive tests than NHWs [2, 5, 21], although the rates of cognitive

decline are similar between the racial groups [5]. However, it should be highlighted that diagnostic tests may not be accurate or generalizable to racial groups outside of NHWs. For example, the Mini-Mental State Examination was found to have a much higher rate of false-positive diagnosis of cognitive impairment in AAs than NHWs [9]. Interestingly, despite these differences, AAs live longer with AD and related dementias than NHWs [2, 7].

AD is well-known for two primary neuropathological hallmarks: Aβ plaques and tau tangles. However, there are no significant differences in Aβ plaques and tau tangles in the brains of AAs and NHWs [9, 22–24]. AAs are more likely to present with mixed AD and other dementia pathologies, particularly Lewy body dementia, infarcts, and cerebrovascular disease [22, 25]. These findings suggest that other factors such as socioeconomic differences, genetic risk factors, and comorbidities have substantial contributions to higher incidence of AD in AAs. The following sections examine the roles of genetics and comorbidities in the racial disparities of AD with a specific focus on the involvement of lipid metabolism. An examination of socioeconomic factors is beyond the scope of this review, and we refer readers to other reviews [3, 26, 27].

1.2.1 Comorbidities

Comorbidities describe health conditions that can increase an individual's risk for diseases, such as AD. Traumatic brain injury, stroke, dyslipidemia/hypercholesterolemia, cardiovascular disease, T2DM, obesity, and hypertension (HTN) all increase risk of AD (Fig. 1.2) [2, 6, 28–32]. These comorbidities also disproportionately affect AAs compared to NHWs. Findings from the Atherosclerosis Risk in Communities (ARIC) study suggest racial disparities in brain aging may be due to differences in risk factor presence, severity, and control [5]. Notably, alterations in lipid metabolism are common in AD and these comorbidities in AAs, which suggests that lipid metabolism may be an important underlying cause of racial disparities of AD.

1.2.1.1 Dyslipidemia

Dyslipidemia is a group of lipid disorders that present due to genetic predisposition or underlying events, such as insulin resistance, excess weight, and hypothyroidism. These events result in abnormal levels of high-density lipoprotein (HDL), low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), and triglycerides [32]. Clinically, dyslipidemia is noted by total cholesterol ≥240 mg/dL, LDL ≥160 mg/dL, HDL ≤40 mg/dL, or the use of lipid-lowering medications [33] and includes high cholesterol levels (hereafter referred to as hypercholesterolemia).

The connection between AD and cholesterol has been firmly established (Fig. 1.3) and discussed in the literature on multiple occasions [13–15, 34]. In the

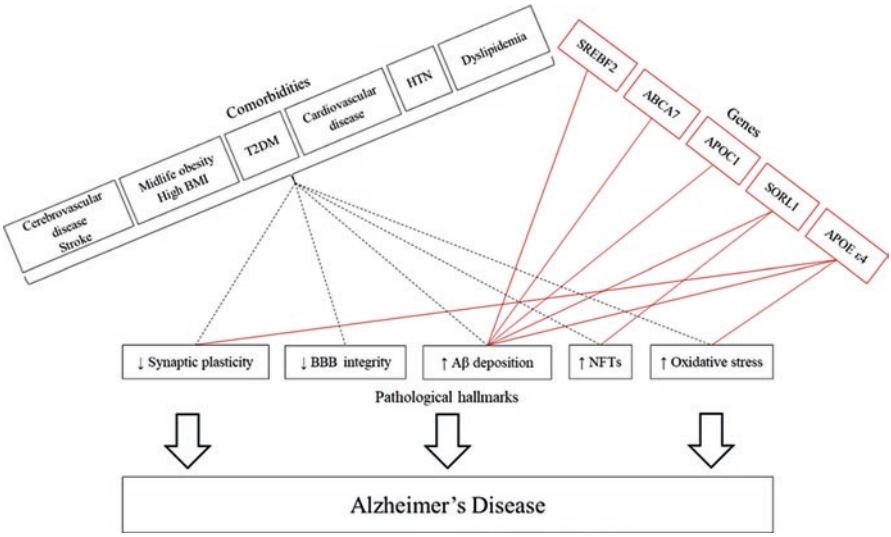

Fig. 1.2 The connections among AD risk factors (genes in red and comorbidities in black) with altered lipid metabolism and AD pathological hallmarks

brain, cholesterol is produced in astrocytes and is transported to neurons by apoE, a process necessary for neurons to form functional synapses [17]. Both increased and decreased levels of cholesterol in the brain have been suggested to contribute to Aβ production [16], and cholesterol accumulates in both Aβ plaques and tau tangles [17]. Brain cholesterol is synthesized de novo, is present in several forms including cholesterol esters, and greatly impacts Aβ monomer formation and aggregation. Peripheral cholesterol levels which come from new synthesis or dietary uptake are also implicated in AD. AD patients have peripheral lipoprotein profiles (i.e., high total plasma cholesterol and LDL and low HDL level) similar to dyslipidemia [32, 35]. This is likely due to a compromised blood-brain barrier (BBB) in AD which would allow HDL to leak from the periphery into the brain, whereas VLDL/LDL is not transported across this barrier (Fig. 1.3).

Dyslipidemia was associated with increased Aβ plaque burden in a Japanese population, even when adjusting for APOE ε4 genotype [31]. In a cohort of AAs without ε4 alleles, higher mean serum total cholesterol levels were observed in individuals with AD compared to those that were cognitively normal [36]. Consistent with these observations, hypercholesterolemia has been associated with AD [17, 30] and in midlife is associated with increased MCI risk later in life [11]. Transgenic mouse studies suggest that the mechanism by which hypercholesterolemia increases AD risk is acceleration of Aβ deposition in the brain [32]. On the other hand, in a meta-analysis of modifiable risk factors for AD, there was no association between high cholesterol levels and incidence of AD [37]. This could be due to the necessity for APOE ε4 dependence.

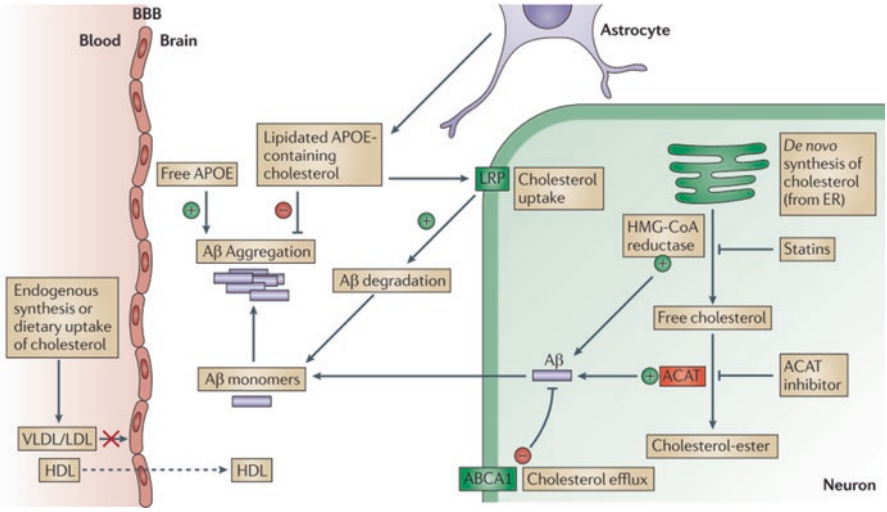

Fig. 1.3 Role of cholesterol in Aβ pathology in AD. ApoE is also included in this figure as it is a cholesterol transporter. Proteins highlighted in green decrease Aβ pathology; proteins highlighted in red increase Aβ pathology. Abbreviations: *ACAT* acyl-CoA:cholesterol acyltransferase 1 (also known as sterol *O*-acyltransferase), *LRP* LDL receptor-related protein, *HMG-CoA* 3-hydroxy-3-methylglutaryl-CoA. Source: See Ref. [34]

Contradictory findings regarding cholesterol levels in AAs and NHWs exist. In an ARIC study, AAs and NHWs did not have different cholesterol levels in midlife (50–60 years old) [38], consistent with a report that lipid profiles between AAs and NHWs are not significantly different on a national level [33]. However, over the age of 45, there is higher incidence of dyslipidemia in AAs compared to NHWs [39]. This incidence is more noticeable in older age groups (i.e., 65–74 years old). Others have found that AAs have higher levels of hypercholesterolemia than NHWs [11]. Together, the discrepancy in these reports requires more evaluation of cholesterol and dyslipidemia levels in AAs but, more importantly, highlights that the role of dyslipidemia in AAs with AD warrants further investigation.

1.2.1.2 HTN

Dyslipidemia is also a risk factor for HTN. Serum cholesterol levels correlate with both systolic and diastolic blood pressure in individuals with HTN [40]. HTN is independently associated with increased cognitive decline, MCI, and AD [5, 11, 17], and high systolic blood pressure is associated with an increased risk of AD [37]. Midlife HTN is associated with increased AD and dementia risk later in adult life [41]. Higher systolic blood pressure increases the odds of brain infarcts and is associated with an increased number of NFTs in postmortem brain tissue [42]. HTN among AAs is likely to increase risk for certain neurovascular pathologies, such as cerebral amyloid angiopathy, white matter lesions, and vascular endothelial

damage [6]. The Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension study recently discovered that reducing systolic blood pressure to less than 120 mmHg decreased MCI risk by 19% in a study cohort that was 30% AA and 10% Hispanic. Importantly, this study implicates treatment of HTN as an effective measure to prevent dementia and AD in multiple racial groups [43, 44].

It is well-known that HTN is more prevalent in AAs than in NHWs [5, 6, 9, 11, 45, 46]. The prevalence of HTN, including diagnosed and undiagnosed cases, in AA men is 42.4% and in AA women is 45% in the United States, and these are 10–12% higher than those for NHWs and Mexican Americans [33]. HTN occurs at an earlier age of onset in AAs [46, 47]. Interestingly, AAs are less likely to have their blood pressure under control when compared to NHWs and Hispanics, despite the fact that AAs are more aware of their HTN and take medications [33, 45, 48]. Increases in systolic blood pressure increase risk of stroke, congestive heart failure, and end-stage renal disease in AAs [46]. Furthermore, in individuals with AD, there is a higher prevalence of HTN in AAs compared to NHWs [6, 21, 25].

The American Heart Association states that HTN is the "most potent risk to cardiovascular health of African Americans" [33]. There is an apparent intersection of HTN and dyslipidemia as risk factors for cardiovascular disease and AD such that progress made with mechanistic understanding of both of these risk factors can have a positive impact on human health, especially among AAs.

1.2.1.3 Obesity

Obesity can lead to inflammation in the brain, compromised BBB integrity, and changes in neuronal structure, synaptic plasticity, and memory [32]. Both low and high body mass indices have been associated with cognitive impairment and dementia [2]. A higher body mass index (BMI, $\geq$30 kg/m^2) in midlife is associated with increased dementia and AD risk, presumably due to increased amyloid deposition [23]. On the other hand, a higher BMI in late life reduces risk of cognitive decline and dementia [41]. A high BMI and obesity are more prevalent in AAs [2], and AAs have higher obesity rates than NHWs at various ages [33, 38]. BMI has stronger effects on other conditions, especially diabetes, metabolic syndrome, and HTN in AAs [2]. Highlighting these aspects of obesity is necessary as high BMI and obesity, HTN, and T2DM are comorbidities of AD.

1.2.1.4 T2DM

Comprehensive discussions of the connections between T2DM, lipid metabolism, and AD can be found in several reviews [49–52]. Briefly, early in the pathogenesis of T2DM, insulin resistance causes lipid accumulation in skeletal muscle and the liver [51]. On the other hand, chronic elevation of free fatty acid levels in plasma can cause insulin resistance and development of T2DM [50]. Circulating triglycerides affect insulin transport across the BBB [49]. T2DM has been associated with

AD [30, 32, 52] and confers significantly increased AD risk [32, 41]. T2DM results in lower insulin and insulin receptor levels, which impairs synaptic function and decreases memory formation [32]. Prediabetes and T2DM are associated with increased cognitive decline [53], vascular dementia, and compromised BBB integrity [49]. A dysfunctional BBB could result in increased brain insulin levels and thus prevent Aβ clearance and degradation.

The associations between T2DM and AD are unaffected by the presence of the APOE ε4 allele [54]. However, the APOE ε4 allele has been linked to decreased expression of insulin-degrading enzyme, which could increase brain insulin levels and contribute to AD pathology as aforementioned. T2DM also increases risk of progression from MCI to dementia [18, 32] and is associated with cognitive impairment. Cognitive impairment is more severe with longer duration of diabetes, poorer control, presence of complications, and comorbid HTN or depression [49]. T2DM is associated with lower cognitive scores at baseline and at a 6-year follow-up in a multiethnic cohort [55], and in another cohort coexisting T2DM was found to accelerate AD pathogenesis [30].

There have been conflicting findings regarding the association of T2DM with AD pathology in the brain [18, 49]. Although systemic insulin resistance has been associated with brain Aβ via PET imaging [56], most studies found no relationships between AD neuropathology and T2DM [57, 58]. In a cross-sectional study of older Brazilian adults, although there was no overall association between AD neuropathology and T2DM, a higher NFT burden was detected when both T2DM and the APOE ε4 allele were present [57]. However, T2DM has been linked to cerebral infarcts, cerebrovascular pathology [59–61], and stroke [54].

T2DM is more prevalent in AAs [2, 5, 33, 62, 63] and Hispanics [6, 9] than NHWs. Prevalence estimates for T2DM in AAs range from 1.4 to 2.3 times higher than in NHWs [11, 63]. According to the National Health and Nutrition Examination Survey, the prevalence of combined diagnosed and undiagnosed T2DM is 21.8% in AAs and 11.3% in NHWs, and over one-third of the cases in AAs were undiagnosed [33]. T2DM was associated with greater cognitive decline in AAs [64], while a study of the Minority Aging Research Study and Memory and Aging Project cohorts found similar effects of diabetes on cognition in AAs and NHWs [65]. Glucose levels in AAs with T2DM were significantly higher than those in AAs who did not develop dementia. These levels then declined prior to dementia diagnosis, while glucose levels remained stable in NHWs with T2DM [66, 67]. Although most evidence supports the existence of racial disparities in T2DM, one study did not find an association between T2DM and race [57].

1.2.1.5 Vascular Diseases

Vascular diseases, which encompass cardiovascular disease, heart disease, atherosclerosis, vascular dementia, and cerebrovascular disease, also involve dysregulated lipid metabolism and thus should be briefly addressed. Vascular pathology increases dementia risk [68]. In a study of MCI and cognitively unimpaired individuals, increased vascular risk factors—measured by Framingham Stroke Risk Profile

score taking into account age, systolic blood pressure, anti-HTN medications, T2DM, smoking, cardiovascular disease history, and atrial fibrillation—were associated with increased cognitive decline [69]. Vascular risk factors increased risk of conversion from MCI to AD, and treatment of these risk factors reduced risk of conversion [70]. History of coronary artery disease and myocardial infarction are also associated with higher dementia rates and more Aβ plaques in the brain [6]. Cerebrovascular disease is more commonly comorbid with AD than other neurodegenerative diseases and when combined can manifest in earlier clinical symptoms of dementia [71]. Surprisingly, in a meta-analysis, stroke was found to have no effect or a negative effect on AD risk [37], which is in contrast to a study reporting that stroke increases AD risk especially in the presence of HTN and T2DM [29].

AAs and Hispanics have a 2.4 and 2 times higher incidence of stroke compared to NHWs [6], and stroke mortality rates for AAs are also 4.5 times higher than in NHWs [33]. These racial differences are exacerbated in younger age groups such as 45–59-year-olds in AAs [72, 73]. There are conflicting reports on whether or not stroke increases the likelihood of developing AD and related dementias in AAs [3, 6, 74]. Atherosclerosis is associated with increased risk of AD [37] and is commonly detected in the brain [75]. A larger proportion of dementia cases are attributed to vascular dementia in AAs and Asian Americans/Pacific Islanders than NHWs and Hispanics [3, 6].

Overall, the prior sections grossly demonstrate that comorbidities greatly influence risk of AD, incidence of AD especially among AAs, and disease pathogenesis. Several of the comorbidities discussed clearly implicate lipid metabolism as a primary feature of the comorbid disease and of AD.

1.2.2 Genetics

Genetic factors are well-known to play a role in AD risk (Table 1.1) and most likely also contribute to racial disparities in AD. Although there is no evidence for a separate genomic region with a different contribution to age-related cognitive decline between NHWs and AAs [76], risk genes such as APOE, ABCA7, and others have been discovered. Frequency of risk alleles and single-nucleotide polymorphisms (SNPs) for these genes, as well as strength of their association with AD, varies among racial groups, and in some cases, there are SNPs and genes that are only associated with AD for a given racial group. Many of these genetic risk factors for AD are related to lipid metabolism (Fig. 1.4), which will be discussed in detail in the remainder of this section.

1.2.2.1 APOE ε4

The APOE gene codes for the protein apolipoprotein E (apoE), which is one of the most abundant lipoproteins in the central nervous system. The primary function of apoE is to maintain lipid and cholesterol homeostasis in the brain, which it

Table 1.1 Genes known to increase risk of AD

Gene	Disease-associated SNP/allele	References
ABCA1[a]	SNPs rs2230806, rs4149313, rs2230805, rs2230808	Wavrant-De Vrièze et al. [77]; Koldamova et al. [78]; Fehér et al. [79]
ABCA7[a]	SNPs rs11550680, rs142076058, rs3764647, rs3752239, rs3764650, rs3752246, rs78117248, rs4147929	Aikawa et al. [80]; Almeida et al. [81]; Hollingworth et al. [82]; Naj et al. [83]; Cuyvers et al. [84]; Lambert et al. [85]
APOC1[a]	Insertion/deletion polymorphism rs11568822, H2 allele	Zhou et al. [86]; Petit-Turcotte et al. [87]; Ki et al. [88]
APOD[a]	Intron 1 polymorphism	Desai et al. [89]
APOE[a]	ε4 allele	Barnes and Bennett [2]; El Gaamouch et al. [16]; Martins et al. [15]; Zhao et al. [90]
BIN1[a]	SNPs rs55636820, rs7561528, rs744373	Reitz et al. [91]; Reitz and Mayeux [92]; Hollingworth et al. [82]; Naj et al. [83]; Seshadri et al. [93]
CD2AP	SNP rs9349407	Naj et al. [83]
CD33	SNPs rs3826656, rs3865444	Bertram et al. [94]; Hollingworth et al. [82]; Naj et al. [83]
CLU[a]	SNPs rs11136000, rs1532278	Lambert et al. [95]; Naj et al. [83]; Harold et al. [96]; Seshadri et al. [93]
CR1	SNPs rs3818361, rs6656401, rs6701713	Hollingworth et al. [82]; Lambert et al. [95]; Naj et al. [83]
EPHA1	SNPs rs11771145, rs11767557	Hollingworth et al. [82]; Naj et al. [83]; Seshadri et al. [93]
MS4A gene cluster	SNP rs610932 in MS4A6A SNP rs670139 in MS4A4E SNP rs4938933 in MS4A4A	Hollingworth et al. [82]; Naj et al. [83]
PICALM[a]	SNPs rs561655, rs3851179	Reitz and Mayeux [92]; Harold et al. [96]; Seshadri et al. [93]
SORL1[a]	SNPs rs2298813, rs2070045, rs668387, rs689021, rs641120, rs1784933, rs3824966, rs12285364	Rogaeva et al. [97]; Lee et al. [98]; Chou et al. [99]
SIGMAR1[a]	Long runs of homozygosity in Chr4q313, 15q24.1, 3p21.31 regions	Ghani et al. [100]
SREBF2[a]	SNP rs2269657	Picard et al. [101]

[a]Related to lipid metabolism

accomplishes via phospholipid and cholesterol transport. ApoE is responsible for delivery of phospholipids and cholesterol to neurons and various receptors for utilization or clearance [15–17]. The transport of cholesterol to neurons is particularly important for synapse formation and neuronal functioning [17]. In addition to carrying lipids, apoE also has the ability to bind Aβ and aid in its clearance from the brain (Fig. 1.3) [15].

While the APOE ε2 allele has a protective effect against AD [15–17, 90, 102], the APOE ε4 allele is one of the strongest genetic risk factors for AD [2, 15–17, 90, 102]. The ε4 allele exerts a dose-dependent effect on AD risk. One ε4 allele confers

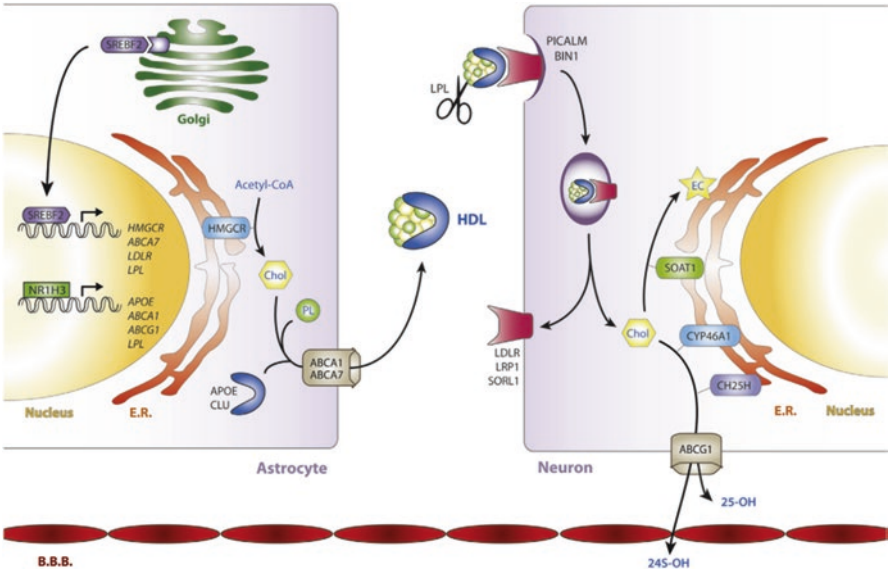

Fig. 1.4 Representation of cholesterol metabolism in the brain, including several AD risk genes and their gene products (source: see Ref. [101])

2 to 3 times greater risk of developing AD, while two ε4 alleles leads to a 12 times greater risk for AD [103]. The ε4 allele has been associated with increased Aβ accumulation and deposition in the brain and cerebral vessels [90, 102, 104], as well as increased tau tangles [2, 18]. Interestingly, individuals with T2DM and the APOE ε4 allele had more of both types of neuropathology than individuals with neither or only one of these factors [105]. APOE ε4 has also been associated with an earlier age of onset of AD [16, 102], more rapid rate of cognitive decline [16], decreased cognitive performance, and increased memory decline [106]. The ε2, ε3, and ε4 alleles lead to three corresponding protein isoforms of apoE, which have different abilities to carry lipids and bind Aβ. ApoE4 is less effective at binding and clearing Aβ from the brain than apoE2 and apoE3 [15, 16, 32, 107]. Additionally, the apoE4 isoform increases both Aβ production and fibril formation compared to the other two isoforms [90, 104]. The apoE4 isoform also suppresses synaptic protein expression, which impairs synapse transmission and plasticity and could contribute to synapse dysfunction and loss that occurs early in AD pathology [90, 102]. ApoE4 is less protective against oxidative stress than the other isoforms and leads to increased dysfunction of cholinergic neurons in AD [15, 16]. APOE ε4 has also recently been associated with vascular pathologies, such as cerebral microbleeds, white matter lesions, and coronary artery calcification, which provides a link between genetic and comorbid risk factors for AD [108].

Disparities in APOE allele frequency and association with AD have been noted among racial groups. Multiple studies have determined that there is an increased frequency of the ε4 allele in AA populations compared to NHWs [2, 25], and the ε4/ε4

genotype has also been reported as more common in AAs than NHWs [25]. On the other hand, another study notes that the frequency of the ε4 allele varies in AAs from about 17 to 21% [9], while in a Florida study of Ashkenazi Jewish, Hispanic, NHW, and AA individuals, no racial differences in the frequency of the APOE ε4 and ε2 alleles were found [6]. APOE ε4 has been associated with increased risk of AD in AAs, although some studies have concluded that it is inconsistently related to AD and cognition in AAs [2, 3]. In addition to being inconsistent, the strength of the association between the APOE ε4 allele and AD is weaker in AAs than NHWs [3, 6]. In support of this, the Washington Heights-Inwood Community Aging Project study found that AAs and Hispanics with at least one ε4 allele were about as likely as NHWs to develop AD, but AAs and Hispanics without an ε4 allele were two to four times more likely to develop AD than their NHW counterparts [6]. Overall, the APOE ε4 allele has a significant contribution to AAs with AD despite contradictory findings and represents a major protein in lipid-related pathways critical for AD pathogenesis.

1.2.2.2 ABCA7

The ABCA7 protein, coded for by the ABCA7 gene, is a transmembrane protein that is an important transporter of lipids through the cell membrane energetically driven by ATP binding [80]. ABCA7 is particularly important for cholesterol and phospholipid efflux mediated by apolipoproteins and through these interactions functions in the biosynthesis of HDL and is involved in the lipidation of apoE [16, 91]. Additionally, there are direct links between ABCA7 and AD, as ABCA7 can affect APP transport through the cell membrane and is involved in the Aβ clearance pathway [80, 91]. For example, overexpression of ABCA7 leads to decreased Aβ levels. On the other hand, deletion of ABCA7 accelerates Aβ production (likely by allowing APP endocytosis), impairs Aβ clearance, and increases Aβ plaque burden [16, 80]. The changes in ABCA7 function due to AD risk mutations are not entirely known. The ABCA7 deletion rs142076058 may result in a frameshift mutation that either causes synthesis of an aberrant protein or nonsense-mediated decay of the truncated RNA transcript [109]. Either of these consequences would likely result in reduced ABCA7 levels and have similar effects to those of the ABCA7 deletion described above. An additional study hypothesizes that the rs3764650 SNP decreases ABCA7 expression before AD onset which increases AD risk, and after AD onset ABCA7 expression increases [110].

Many SNPs within the ABCA7 gene have been associated with AD (Table 1.2), although premature termination codon mutations and loss-of-function mutations have also been noted [80]. AD risk conferred by ABCA7 has been confirmed specifically in AAs, and the association is stronger and more widespread in AAs than NHWs [2, 91, 111]. A genome-wide association study (GWAS) supports this in that SNP rs115550680 is significantly associated with AD in AAs with an effect size (70–80%) comparable to that of APOE ε4 [91, 92]. Notably, many of the ABCA7 SNPs are present and confer risk in one specific racial group. For example, a dele-

Table 1.2 ABCA7 SNPs associated with AD in AAs

SNP	Populations associated with AD	Sources
rs3752239	AAs	Aikawa et al. [80]
rs3752246	Multiple racial groups	Naj et al. [83]
rs3764647	AAs	Aikawa et al. [80]
rs3764650	NHWs, AAs	Almeida et al. [81]; Hohman et al. [111]
rs115550680	AAs	Reitz et al. [91]; Reitz and Mayeux [112]
rs142076058	AAs, rare in NHWs	Cukier et al. [109]; Aikawa et al. [80]

tion in ABCA7 (rs142076058) is significantly associated with AD, which was commonly identified in AA cases and controls (15.2 and 9.74%, respectively) but only in 0.12% of NHWs [109]. There are more SNPs (rs3764647, rs142076058, rs3752239) that have only been associated with AD in AAs, while rs3764650 is associated with AD in both NHWs [80, 81] and in individuals with more African ancestry [111]. These findings provide clear evidence that ABCA7 is likely a contributing factor to the racial disparities in AD, as ABCA7 is a stronger genetic risk factor for AD in AAs than NHWs.

1.2.2.3 Other Genes

In addition to APOE and ABCA7, other AD risk genes include bridging integrator 1 (BIN1), clusterin (CLU), phosphatidylinositol binding clathrin assembly protein (PICALM), sortilin-related receptor 1, ABCA1, L(DLR) class A-type repeats containing (SORL1), apolipoprotein D (APOD), apolipoprotein C1 (APOC1), sigma non-opioid intracellular receptor 1 (SIGMAR1), and sterol regulatory element binding transcription factor 2 (SREBF2) [79, 86, 89, 92, 98, 100, 101]. For the purpose of this review, only those genes related to lipid metabolism will be discussed. Lipid-related AD risk genes involve pathways such as regulation of Aβ formation (ABCA7, APOE, ABCA1, CLU, PICALM, SORL1), regulation of NFT assembly (APOE, CLU, SORL1), and protein-lipid complex assembly (ABCA7, ABCA1, APOC1, APOE, BIN1) [113]. BIN1, CLU, and PICALM are less common risk genes. Clusterin, also known as apolipoprotein J, has functions that parallel those of apoE, while both BIN1 and PICALM are involved in receptor-mediated endocytosis, which is important for lipid internalization and transport including transport mediated by apoE and clusterin [114]. In a GWAS study of AAs, AD-associated SNPs in BIN1, CLU, and PICALM had a 10–20% increase in AD risk and significantly lower effect sizes than in NHWs [92]. This result is confounded by another GWAS study that shows CLU and PICALM are not associated with AD in AAs but that BIN1 is associated with SNPs in AAs that differ from those in NHWs [91]. ABCA1 has functions similar to ABCA7 in apolipoprotein transport and Aβ clearance. In an AD mouse model, deficiency of ABCA1 increases Aβ deposition in the brain and decreases apoE levels, while ABCA1 overexpression decreases Aβ deposition [115, 116]. Interestingly, the effect of ABCA1 on Aβ was APOE genotype-dependent as

ABCA1 deficiency reduced Aβ clearance in APOE4 mice but not in APOE3 mice [115]. Several SNPs in ABCA1 have been associated with AD in various populations including NHWs, Swedish, and Chinese [77–79], although no data were available for AA groups. SORL1 is involved in the regulation of lipoprotein lipase trafficking, APP processing and trafficking, and tau cellular processes, and its expression is reduced in AD brains [97, 99, 117]. Various SNPs and haplotypes in SORL1 have been associated with AD in NHWs, Hispanics, AAs, and Asians, although these genetic variations are not the same across racial groups [97–99].

Other potential genetic risk factors for AD in AAs exist. ApoD, similar in function to apoE, has four polymorphisms in the APOD gene unique to individuals of African ancestry and is associated with increased risk of AD [89]. ApoC1 is known to interfere with apoE receptor interactions and thus decreases clearance of lipoproteins containing apoE [87]. ApoC1 also can inhibit the cholesteryl ester transfer protein and activate lecithin-cholesterol acyltransferase and thus cholesterol esterification. Although the APOC1 gene is located adjacent to the APOE gene, the H2 allele of APOC1 was found to be a risk factor for AD independent of APOE ε4. These two alleles occur frequently together in AD populations and combined produce higher AD risk than either allele individually [87, 88]. Decreased levels of apoC1 mRNA with the H2 allele and increased apoC1 protein levels have been reported in AD [87]. Additionally, an insertion/deletion polymorphism in the APOC1 gene was found to increase AD risk in NHWs, Asians, and Caribbean Hispanics, but not in AAs [86].

Long runs of homozygosity in genes in AAs are associated with AD. The most notable of these genes is SIGMAR1 which encodes a protein that functions in lipid transport from the ER and helps to regulate various cellular functions via regulation of biosynthesis of lipid microdomains in the membrane [100]. Lastly, SREBF2 is a protein involved in lipid homeostasis and cholesterol biosynthesis with activity affected by brain cholesterol levels. SNP rs2269657 of SREBF2 was associated with AD pathological biomarkers and gene expression levels in the Alzheimer's Disease Neuroimaging Initiative cohort, which includes individuals of multiple ethnic backgrounds [101]. In summary, there are several genes critical to lipid metabolism, which have reported risk for AD, especially in AAs, and these warrant further investigation.

1.3 'Omics Approaches to Study Lipid Metabolism in AD

Review of the current literature involving lipid metabolism and AD reveals gaps that remain in our molecular understanding of AD, particularly across different racial groups. Some studies have focused on one or a few genes, proteins, and lipids in lipid metabolism pathways in AD. For example, a study on plasma levels of total cholesterol, HDL, LDL, and triglycerides revealed that higher midlife total cholesterol and triglycerides levels were associated with increased 20-year cognitive decline in NHWs but not in AAs [118]. In another study, apolipoproteins J, E, A-I,

and C-III and their subspecies were measured with ELISA in plasma samples from the Ginkgo Evaluation of Memory Study cohort [119]. Higher apoE and apoA-I levels were associated with lower Aβ deposition and lower hippocampal volume, respectively. Lower plasma apoE levels were associated with higher Aβ deposition [120]. Heart-type fatty acid-binding protein was increased in cerebrospinal fluid (CSF) of AD patients [121]. Western blots have been used to study phospholipase D1 in AD brain tissue as well, which found elevated levels [122]. Neurodegenerative markers in AD brain tissue were recently measured in AAs although these markers are not related to lipid metabolism [123].

The limited focus of one or a few targeted species prevents a comprehensive picture of the changes occurring in the lipid metabolism pathway in AD from being gained. 'Omics approaches including genomics, proteomics, metabolomics, lipidomics, and transcriptomics enable comprehensive analyses of their respective molecule classes and can fill these gaps in our understanding of lipid metabolism. It is especially important to note that a majority of 'omics studies in AD are focused on NHWs or other majority populations and grossly exclude AAs. This presents an opportunity for the field to ensure that 'omics studies are more racially inclusive.

Discovery-based 'omics approaches are used for broad studies that can help with disease understanding and biomarker discovery [124, 125]. Several studies have utilized discovery-based proteomics to study AD for various purposes, such as to examine changes in the overall proteome in aging and MCI or AD [126–140] and to study proteins associated with oxidative stress [141–145]. Discovery-based proteomics of AD and Parkinson's disease brain tissue samples identified a combined total of 11,840 proteins [146]. The power of such studies is deep proteome coverage, which leads to insights on many biological pathways in health and disease. We refer the reader to several recent reviews on proteomics studies in AD [147–149].

On the other hand, 'omics approaches can also be targeted, enabling the focused study of a few to a few hundred species. Targeted proteomics has been used to analyze CSF samples in AD for potential biomarkers in several instances [148, 150–152]. Targeted proteomics in the brain identified several proteins with expression levels that correlated with Aβ and tau pathology [149, 153–156]. Targeted proteomics has also been used to specifically study proteins involved in lipid metabolism, mainly apolipoproteins in blood and blood-based bio-specimens [151–159]. One targeted proteomics assay was developed to analyze 12 apolipoproteins in serum or plasma samples, which identified significant effects of gender and use of lipid-lowering medications on apolipoprotein levels [157]. Few examples of targeted proteomics applied to study lipid metabolism in AD exist. A two-dimensional gel electrophoresis analysis quantified three fatty acid-binding proteins in AD and observed decreased levels in AD brain [160]. Serum protein analysis showed that there was no significant difference in apoE levels in MCI patients and controls [161]. Targeted lipidomics has been used to study changes in ceramide levels in human neurons in response to a neurotoxic signaling glycerophospholipid [162]. Targeted metabolomics has been used to measure 188 lipid and metabolite species in plasma samples from a subset of mostly AA participants in the ARIC study [163]. The metabolomics results from this study are particularly interesting because ten of

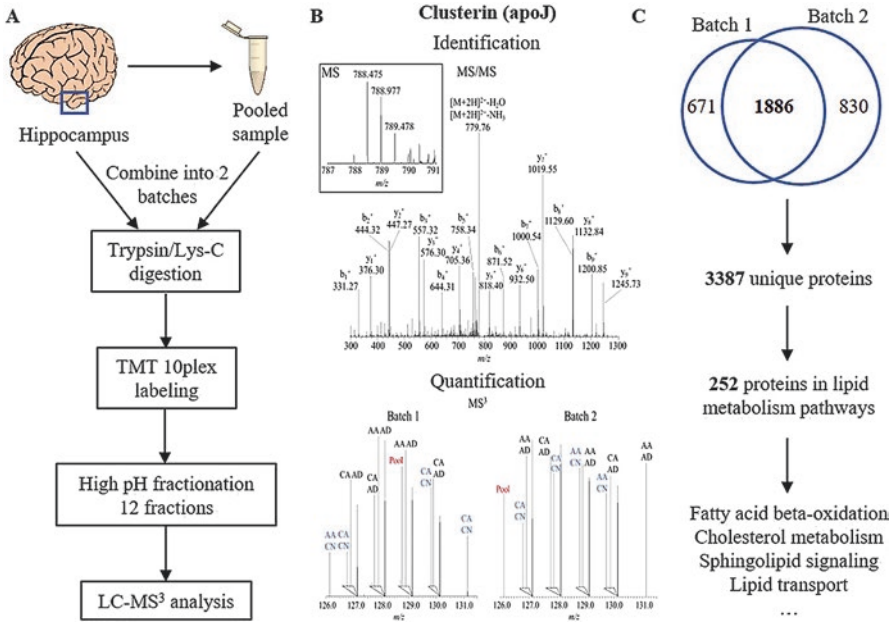

Fig. 1.5 Summary of our hippocampal proteomics experimental workflow (**a**), example MS, MS/MS, and MS^3 spectra from a lipid metabolism protein (clusterin) (**b**), and an overview of our protein identifications from these analyses (**c**) whereby two independent batches of TMT-tagged samples were analyzed. Abbreviations: *TMT* tandem mass tags, *LC* liquid chromatography, *MS* mass spectrometry. Unique proteins were identified in either or both batches of samples

the species that had been previously found to be predictive of MCI or dementia in NHWs were not predictive of either condition in this mostly AA cohort.

Multi-omics, or the integration of multiple types of 'omics data, can provide a more complete picture of the biological system being studied and allow determination of changes potentially associated with disease pathogenesis, biomarker discovery, and therapeutic targets [164–167]. Several studies have applied such methods in investigations of AD by using proteomics in combination with genome and transcriptome data to identify potential pathways or networks that may contribute to AD pathogenesis [168–170].

Our laboratory has demonstrated the use of multi-omics, specifically proteomics and lipidomics, to study lipid metabolism in AD across racial groups (manuscripts in preparation). In a pilot AD study, we have analyzed postmortem hippocampal tissues using a quantitative proteomics workflow (Fig. 1.5a). The workflow applies tandem mass tagging (TMT) of tryptic peptides to liquid chromatography-mass spectrometry (LC-MS), tandem MS, and MS^3 on an Orbitrap Fusion Lumos mass spectrometer. This comprehensive workflow enables peptide identification from the MS/MS spectra and accurate relative quantification from the MS^3 spectra (Fig. 1.5b). From this study we identified over 3300 proteins, which included 252 lipid-related proteins (Fig. 1.5c). These lipid-related proteins encompass many pathways includ-