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A global view of the genetic basis of Alzheimer disease

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Abstract

The risk of Alzheimer disease (AD) increases with age, family history and informative genetic variants. Sadly, there is still no cure or means of prevention. As in other complex diseases, uncovering genetic causes of AD could identify underlying pathological mechanisms and lead to potential treatments. Rare, autosomal dominant forms of AD occur in middle age as a result of highly penetrant genetic mutations, but the most common form of AD occurs later in life. Large-scale, genome-wide analyses indicate that 70 or more genes or loci contribute to AD. One of the major factors limiting progress is that most genetic data have been obtained from non-Hispanic white individuals in Europe and North America, preventing the development of personalized approaches to AD in individuals of other ethnicities. Fortunately, emerging genetic data from other regions – including Africa, Asia, India and South America – are now providing information on the disease from a broader range of ethnicities. Here, we summarize the current knowledge on AD genetics in populations across the world. We predominantly focus on replicated genetic discoveries but also include studies in ethnic groups where replication might not be

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feasible. We attempt to identify gaps that need to be addressed to achieve a complete picture of the genetic and molecular factors that drive AD in individuals across the globe.

Introduction

The rapid increase in the prevalence of dementia worldwide is considered by many to be a global emergency[1]. As we enjoy the benefits of longer lives, we face the blunt reality that dementia affects over 30% of those aged 80 years or older[1]. Estimations from the WHO suggest that around 55 million people globally have dementia, of whom 40 million are thought to have Alzheimer disease (AD) and over 60% live in low-income and middle-income countries. As the proportion of older people in the population increases in nearly every country, the total number of individuals with AD is projected to rise to approximately 78 million by 2030 and possibly 139 million by 2050. Currently, 6.5 million American individuals are living with AD, which equates to nearly 11% of the population of the USA. By 2050, this number is expected to have doubled to 13.8 million. The risk of late-onset AD increases with age, a family history of the disease and the presence of genes associated with the disease[1]. With no cure or prevention strategy on the horizon, countries worldwide seek ways to provide humane care for those affected at a cost that is sustainable.

The genetics of Alzheimer disease

Complex genetic disorders, such as AD, are likely to be solved by identifying variants predisposing to disease. These variants and the genes in which they lie can be investigated to determine the mechanisms by which they cause disease. Functional studies can then be performed to yield targets for therapeutic strategies. Over the past four decades, the genetics of AD has been an area of intense interest. According to estimates, 60–80% of the risk of AD is attributable to heritable (genetic) factors[2]. Despite this relatively high heritability, identifying genes that cause AD has proven to be complex, with both rare and common genetic variants contributing to the disease. The accuracy of identifying a specific genetic cause of dementia in an individual depends on the disease phenotype, age at onset and family history.

Prior to the sequencing of the human genome in 2003, the main research strategy was to focus on the rare, autosomal dominant forms of AD that begin in middle age. Family-based analysis methods (Box 1) were amenable to genetic approaches available at that time and mutations in three genes – *APP, PSEN1* and *PSEN2* – were discovered between 1985 and 1995 (refs. 3–6). Since then over 300 pathogenic variants have been identified in these three genes, yet at least 25% of the Mendelian forms of AD remain to be defined[7–9]. Whole-exome sequencing (WES) and whole-genome sequencing (WGS) are now being used to identify additional genes that contribute to these typically highly penetrant forms of the disease. Rare coding variants in *PSEN1* and *PSEN2* have also been found in multiplex families with late-onset disease[10], indicating a genetic continuum between early-onset and late-onset forms. These results suggest that factors other than these variants can affect the age at onset and penetrance of AD[11].

In 1991, Pericak-Vance and colleagues[12] found an association on chromosome 19q that led to discovery of variants in the apolipoprotein E (*APOE*) gene that increase or decrease the risk of the more typical late-onset form of AD. The *APOE* gene has three common allelic forms: ε2, ε3 and ε4. The ε4 allele was found to increase the risk of AD, whereas the presence of the ε2 allele was considered to be protective. This study also demonstrated the power of an association study that compares allele and genotype frequencies in two groups: individuals with AD and individuals without disease (case–control design; Box 1).

Over the three decades since the discovery of the association with *APOE* variants, research has proven that AD is highly heterogeneous with many variants conferring small effects on risk (polygenic)[13]. The success of the *APOE* case–control association design and the relative ease of recruiting individuals with and without AD has led to a multitude of studies that use this approach to identify additional genetic risk factors in populations throughout North America, Europe and Asia. Advances in genomic technology have promoted the case–control approach, which now includes genome-wide genotyping of single nucleotide polymorphism (SNPs) as well as WES and WGS. Analyses can focus on association with SNPs or variants or can evaluate the overall evidence of association with a gene, by aggregating the effect of multiple variants within the gene into one test. With the rapid decline in the cost of WGS and the advent of large national and international collaborations, genetic studies now include samples from hundreds of thousands or even a million participants. Over the past 3 years, studies[14–17] have identified over 70 different genetic variants associated with AD using this approach (Fig. 1). The majority of these variants were identified in non-Hispanic white individuals mostly from Europe and the USA, and might not generalize to non-white and/or Hispanic individuals. Thus, the existing data are unlikely to fully explain the genetic risks among individuals from Africa, Asia, the Middle East, and Middle and South America. In addition, many of the studies in non-white individuals were small and the findings still need replication to be confirmed.

Polygenic risk scores provide a quantitative approach to combine the effect of multiple variants and have proven to be an important tool for defining genetic risk in the presence of many different variants with small individual effects. Polygenic risk scores have been evaluated in epidemiological cohorts to estimate the effect of risk factors in a population-based setting in which the number of cases reflects the population incidence rate (Box 1). A polygenic risk score of the AD-associated genetic variants identified in non-Hispanic white individuals is associated with a faster rate of tau-PET accumulation[18].

Migration, diversity and ancestry

Human migration and geodemographic events have taken place over thousands of years of human evolutionary history, and have shaped the genetic diversity among current populations. Substantial differences in allele frequencies and the extent to which common alleles are inherited together (linkage disequilibrium) can have profound effects on the associations of genetic variants with traits and disease in different populations. The phylogenetic analyses inferred from global human mtDNA sequences[19] almost four decades ago demonstrated that anatomically modern humans originated in Africa and that the population subsequently expanded outwards. The largest split between human populations

occurred around 160,000–110,000 years ago in sub-Saharan Africa[20,21] (Fig. 2). Over the past 10 years, sequencing of genomes of ancient humans[22] and other hominins[23] demonstrated that individuals with a greater degree of African ancestry have less linkage disequilibrium than individuals with a smaller degree of African ancestry[24,25]. This is because, throughout human evolutionary history, the population living in Africa maintained a larger effective size and also had more time for recombination than other populations. By contrast, migration out of Africa within the past 50,000–100,000 years resulted in a distinct genetic pattern of populations living outside Africa showing less genetic diversity with a linear decline of heterozygosity and flattening of the ancestral allele frequency spectrum as a function of geographic distance from Africa and founder event bottlenecks[26]. These events have resulted in individuals with a higher degree of African ancestry having higher levels of genetic diversity than individuals with a lower degree of African ancestry[27]. In most genomic studies, individuals are assigned to genetic ancestry categories through principal component analysis, a multivariate approach intended to characterize individuals and populations by ethnobiological origins and relatedness.

These ancestral differences have implications for the assessment of genotypic risk[28–30]. Although some associations between genetic markers and disease are present across populations – providing important evidence for a shared genetic basis of disease risk – genetic risk prediction models developed from one ancestral group do not perform as well when applied to other ancestral groups[31]. Common variants can be shared globally but rare variants are usually shared by closely related populations and might be restricted to a single continental group[32]. The small group of humans that left Africa about 100,000 years ago and populated the rest of the world carried only a subset of the African variations. Thus, populations throughout the world may have genomes that include variants emerging as part of the African migration worldwide. The period in time and the number of individuals migrating would then determine the degree of African ancestry in a given population. However, the subset of human genetic variation left behind in Africa can be studied only in individuals with a high degree of African ancestry[33].

African American and Hispanic groups, the largest admixed non-European groups in the USA, account for 12.6% and 16.3%, respectively, of the population[34]. The first Africans were brought to North America as slaves in the early 17th century and this continued until slavery was abolished in 1865 by the US Congress. The degree of variability in the number of variants is roughly proportional to the degree of recent African ancestry an individual has in their genome[35]. Thus, for admixed populations, overall genetic disease risk might be determined by multiple genetic variants from a combination of ancestral backgrounds. For admixed groups with African ancestry, it is essential to understand AD risk in indigenous African individuals.

Impact on *APOE* and other genetic associations with AD.—In most genetic studies conducted in individuals of non-European ancestry, participants self-reported their ancestry, and the researchers performed statistical corrections for ancestral heterogeneity (that is, population substratification owing to genetic ancestral background) or adjustments such as principal components. From studies in individuals of African[36–39] and Hispanic ancestry[40–44], notable ancestry-related differences have been identified in the genetic

architecture of AD. Compared with non-Hispanic white individuals, *APOE* ε4-associated AD risk is weaker in individuals with African ancestry but stronger in individuals of Japanese ancestry[45–47]. Preliminary evidence indicates that this variability in risk is driven by the ancestral origin of the DNA at the *APOE* ε4 locus (for example, local genetic ancestry)[48,49]. The *APOE* ε4 amino acid coding sequence does not differ consistently between populations of different ancestry; thus, the source of the variability in genotypic risk associated with *APOE* ε4 could lie in regulatory regions that affect gene expression. Indeed, in a post-mortem study of individuals with AD, higher levels of *APOE* expression were observed in the brains of individuals of European ancestry than in those of individuals of African ancestry[50].

Genome-wide studies of individuals of African ancestry that used population substratification by principal components have identified many genes, including *ABCA7* and *ACE*, that contain ancestrally specific risk variants[36,38,51] (Table 1). In *ABCA7*, a 44 bp deletion was strongly associated with AD in African Americans[52] and also present in Caribbean Hispanic individuals, who are known to have a high proportion of African ancestry (41.8%)[53]. Functional studies suggest that this ancestry-specific deletion might result in increased production of toxic amyloid-β (Aβ) in neurons and a reduced ability to clear Aβ in microglia[52], making it a candidate of interest for development as a therapeutic target. Other rare truncating and splice-altering variants in *ABCA7* confer risk in non-Hispanic white individuals[54–56].

Mutations in *APP, PSEN1* and *PSEN2* have been reported in individuals with early-onset AD from many regions and ancestries, including northern and southern European populations[57,58], various Middle Eastern and Arab populations[59,60], Caribbean Hispanic populations[61–64], Latin American populations[65–67], populations from northern and southern Africa[68–71], populations from Australia and New Zealand[72,73], and a range of Asian populations including those from China, Korea, Taiwan, Japan, India and Malaysia[71,74–80]. Although some variants are shared across populations, most variants are unique to ancestral groups.

Africa

The Alzheimer's Disease International report on dementia in sub-Saharan Africa describes the state of dementia in this region and summarizes several trends with respect to the ageing population[81]. It is noteworthy that of the 46 countries in sub-Saharan Africa, only a small fraction have existing capacity for dementia research and clinical care. Africa comprises mostly low-income to middle-income countries, and the prevalence of AD in the continent is expected to reach approximately 3.5 million by 2030 and 7.6 million by 2050 (ref. 81). Although there are several studies that focus on the epidemiological aspects of AD in Africa, research into the genomics of AD in Africa is in its infancy.

Several candidate gene studies of early-onset AD in Africa identified variants in AD-associated genes previously identified in non-Hispanic white individuals: *APP*, *PSEN1, PSEN2* (refs. 68–70) and *TREM2* (ref. 82). The effect of the *APOE* ε4 allele on AD risk has also been investigated in various groups of individuals with African ancestry[83–87]. A Moroccan study sequenced exons 16 and 17 of *APP* in 17 individuals with sporadic AD

and eight individuals with familial early-onset AD. This included seven novel frameshift mutations and one novel splice mutation identified in exon 17. A similar targeted study of *PSEN1* and *PSEN2* in Moroccan individuals with familial and sporadic AD also identified one novel frameshift mutation in *PSEN1* and two in *PSEN2* (ref. 68). In an investigation of vascular disease-associated polymorphisms in 200 Tunisian individuals with dementia and 300 cognitively healthy Tunisian individuals, polymorphisms in *APOE*, angiotensin-converting enzyme (*ACE*) and paraoxonase 1 (*PON1*) genes were found to be associated with dementia; the association of these variants with AD was not investigated[87].

APOE remains the most studied AD gene in individuals of African ancestry. Its known association and substantial contribution to risk in non-Hispanic white individuals[88] make it the obvious candidate for global investigation. One of the earliest studies of *APOE* among African American individuals living in New York City found no association with AD[89], but subsequent studies of African American individuals from Indianapolis and Yoruban individuals from Ibadan, Nigeria, found an association between the *APOE* ε4 allele and incident AD[83]. However, among the Yoruban individuals, *APOE* ε4 homozygosity, but not heterozygosity, was a significant risk factor for AD, which indicates a weaker effect of the variant in individuals of African ancestry than in non-Hispanic white individuals. A second study of *APOE* in Yoruban individuals surmised that a combination of genetic effects (lack of association with *APOE*) and environmental effects (low cholesterol and lipid levels, and less vascular disease and hypertension, owing to a low-fat diet) might explain the difference[84]. A similar study in a Nigerian community[84] examined the relationship between *APOE* genotype, cholesterol and AD. Individuals met NINCDS–ADRDA[90] criteria for AD, and ICD-10 criteria[91] for vascular dementia and other secondary dementias. However, the study lacked autopsy or biomarker information, leaving the possibility of misdiagnosis. Increased levels of cholesterol and LDL were associated with a higher risk of AD, but only in individuals without an *APOE* ε4 allele. The effect of *APOE* genotype on AD risk has also been investigated in Kenya but no association between *APOE* ε4 and AD risk was observed[85].

The reports of lower *APOE* ε4-associated risk of AD in individuals of African ancestry than in non-Hispanic white individuals have triggered additional ancestry-specific studies[92,93] and studies to identify genetic variants that might lower *APOE* ε4 risk on an African ancestry haplotype. A statistically significant interaction between the *APOE* ε4 allele and the SNP rs10423769 was identified in a discovery dataset from African Americans[36,94], and the finding was subsequently replicated by the same investigators in a large Puerto Rican cohort[42] and the Yoruban cohort mentioned above[95]. The rs1042369_A allele was associated with an estimated 70% reduction in the risk of AD for *APOE* ε4 homozygotes. This African ancestry-specific locus is 2 Mb from the *APOE* locus and is located in a cluster of pregnancy-specific β1-glycoproteins; it might represent a potential therapeutic target for further investigation.

Latin America

The origin of people currently living in Latin America can be traced to extensive admixture between Native American, European and African populations, and the proportions of

different ancestries can vary according to region[96–98]. This historical population structure in Latin America makes genetic association studies challenging because of the ancestral differences that exist among countries and even regions within Latin America. An estimated 8.5% of adults in Latin America aged 60 years and over have dementia[99]. The prevalence of dementia in the region is expected to increase by up to 400% by 2040, greater than the increase predicted in Western Europe or North America[100].

Mutations in *APP, PSEN1* and *PSEN2* that cause early-onset AD have been identified in Caribbean Hispanic individuals[10,61]. In addition, a missense variant in *PSEN1* (NM_000021.3: c.1247T>C p.Ile416Thr), originating on an African haplotype, was identified in individuals from a Colombian admixed population[101] and a variant at codon 280 in *PSEN1* (PSEN1 E280A) was identified in a large Colombian kindred[102]. A phase II clinical trial (NCT01998841) was then performed in individuals with the latter variant to test the efficacy of a monoclonal antibody (crenezumab) against monomeric and aggregated $A\beta_{1–40}$ and $A\beta_{1–42}$ (ref. 103). Although the study did not identify any statistically significant effects of treatment, cognitive, brain imaging and biomarker outcomes showed trends towards favourable outcomes. Compared with non-Hispanic white individuals, among Caribbean Hispanic individuals the effects of *APOE* ε4 homozygosity on AD risk are blunted and there is no increased risk among heterozygotes[43,46].

Genome-wide association studies (GWAS) in Caribbean Hispanic individuals have identified several risk loci near genes known to be associated with AD in non-Hispanic white individuals: *PICALM, CLU, BIN1, MS4A* gene cluster, *CD33, CD2AP, ABCA7* and *EPHA1* (refs. 104–106). Subsequent WES or WGS studies in these individuals have also identified rare AD-associated variants in many other genes such as *TREM2, SORL1, PINX1, PGL2, ABI3, PTK2B* and *AKAP9* (refs. 40,44,48,49,107,108). A study using admixture mapping in a large number of Caribbean Hispanic participants to identify AD-associated ancestral blocks for European, African and Native American ancestral components found four such ancestral blocks located on chromosomes 1, 6, 21 and 22. Fine mapping using these ancestral blocks prioritized the *GCAT* gene on chromosome 22, which was replicated in an independent dataset[109] (Fig. 3). Functional studies in human post-mortem tissue and two model systems (*Drosophila* and zebrafish) suggested that the inflammation-related activity of *GCAT* is a response to amyloid toxicity, and that reduced *GCAT* expression exacerbates AD pathology.

Evidence of genetic interaction effects has also been observed. Among individuals from Mexico, the presence of the *APOE* ε4 allele and variants in *SORL1* implicated a possible genetic interaction effect that increases AD risk[110]. A single mutation in the *PSEN1* gene (E280A) is the cause of the world's largest autosomal dominant AD kindred, located in Antioquia, Colombia. The mutation is virtually 100% penetrant for AD. It is noteworthy that a member of this Colombian family escaped cognitive impairment until her seventies. She also carried two copies of the *APOE* ε3 Christchurch (R136S) mutation[11], suggesting that homozygosity for the *APOE* ε3 allele might be protective.

East Asia

China is likely to have the largest number of individuals with AD in the world. According to a recent meta-analysis, the prevalence of dementia varies from 4.8% in southern China, to 5.2% in central China, 5.5% in northern China and 7.2% in western China; however, not all parts of the country have been surveyed[111]. East Asia has three major ethnic groups: Han Chinese, Japanese and Korean. As in many other populations, mutations in *APP, PSEN1* and *PSEN2* have been identified among individuals with familial early-onset AD across all three groups[77,112]. In addition, candidate gene studies and GWAS have identified AD risk variants in or near several genes that also contain AD risk variants in other ethnic groups[113]. These genes include *APOE, SORL1, SORCS1, TREM2, BIN1, CLU, MS4A4E/MS4A6A, CD33, PICALM, DAPK1, UNC5C, CNTNAP2, SHARPIN* and *KCNJ15*. In Han Chinese individuals, the *TREM2* p.H157Y variant reached an odds ratio of 11.01 in a targeted sequencing study[114] and an odds ratio of ~3.6 in a meta-analysis of over 7,000 individuals with AD and 7,400 healthy control participants[115], indicating the importance of this locus in this population. Additional loci suggested by GWAS or WGS included intergenic regions at *SUDS3–SRRM4* and *FAM47E–SCARB2* in Japanese cohorts; *GCH1, RHOBTB3–GLRX* and *CHODL* in Han Chinese cohorts; and *CHD2, CACNA1A* and *LRIG1* in South Korean cohorts[113,116–121] (Table 2).

Disease-associated loci differ notably among the three ancestral East Asian subgroups (Table 2). Although some of these differences might be explained by limited sample sizes and statistical power, Han Chinese, Japanese and Korean populations have distinct genetic makeups and substantial differences in allele frequencies and linkage disequilibrium patterns, which make the presence of ancestry-specific disease-associated variation likely[122]. We expect that additional variants and loci will be identified in East Asian populations as the results of additional, larger genetic studies begin to be published. Together, these data further highlight the importance of performing genetic studies in non-European populations to identify more effective, ancestry-informed druggable targets[120].

West Asia and the Middle East

Throughout the West Asian and Middle East region, numerous families with early-onset AD and *PSEN1* and *PSEN2* mutations have been identified[123–127]. Mendelian forms of AD with novel phenotypes have also been observed. For example, in two individuals from the same family in Turkey, early-onset AD and spastic paraparesis was found to be associated with a heterozygous splicing variant (c.869-1G>A) in *PSEN1* (ref. 123). In a family in Israel with a history of cognitive decline or intracerebral haemorrhage across seven generations, affected individuals were found to carry a copy number variant (chr21:27,224,097-27,871,284) that included the *APP* locus[126]. A second copy number variant on chromosome 5 co-segregated with the *APP* duplication in some family members. In this large family, asymptomatic carriers showed cognitive decline in their mid-thirties.

The association between *APOE* ε4 and AD in West Asian and Middle East populations is robust, although there are regional differences in *APOE* allele frequencies, specifically a low prevalence of the ε4 allele in some regions[128]. *APOE* ε4 has been strongly associated with AD in cohort and clinical studies from Egypt, Iran, Israel, Lebanon, Saudi Arabia and

Turkey[129–134]. In studies of familial and sporadic AD across the West Asian and Middle East region, associations with AD were confirmed for several established candidate genes: *TREM2, SORL1, ABCA7, ACE, CD2AP, CLU* and *EPHA1* (refs. 124,129,134–141). A protective allelic association in *PICALM* was also reported[142]. Although there have been few large genome-wide investigations of AD in this region, the identification of common variants in known AD genes confirms the global nature of this disease.

Challenges and future directions

Many of the earlier studies discussed above were limited in size and statistical power to detect more than a few genetic associations. Some smaller studies lacked adjustment for population substratification, which might have affected the findings. Environmental factors such as socioeconomic status or access to health care are also likely to have influenced associations between genetic variants and AD. The ascertainment of larger cohorts consisting of individuals with a range of different ancestries, and the investigation of these cohorts with genome-wide arrays and WGS coupled with adjustment for ancestral background and important environmental factors, will be crucial if we are to fully disentangle the genetic and molecular underpinnings of AD.

New collaborative efforts such as the African Dementia Consortium (AfDC)[143] are important milestones towards these goals. The AfDC is a coalition of African dementia researchers that aims to generate a variety of data including clinical, cognitive, epidemiological, socioeconomic, neuroimaging, genomic and biomarker data to characterize and understand AD and related dementias across Africa. The AfDC will work together to define interventions and treatments for dementia across Africa that could also have a worldwide impact. For example, currently only a few African countries have data available on AD prevalence and incidence (Fig. 4). The AfDC will promote research efforts in this area to better characterize the disease across the continent. Genetic studies will also have a key role, with the AfDC collaborating globally to identify new variants for AD, many of which will be unique to African populations. Currently the AfDC includes researchers from nine African countries: Nigeria, Ghana, Benin, Cameroon, Kenya, Uganda, Tanzania, Mozambique and Ethiopia. The AfDC is coordinated from the College of Medicine, University of Ibadan[143], and we consider it to be crucial for future success in both research and clinical care in Africa.

Several new efforts aim to include participants with a range of different ancestries in studies based in the USA. The largest AD DNA sequencing study in the USA is the Alzheimer's Disease Sequencing Project, which conducts both WES and WGS studies, and was designed to identify new risk and protective variants that could help to identify putative therapeutic targets. However, like previous genome-wide array studies, the initial large-scale sequencing studies focused primarily on non-Hispanic white individuals, and included a limited number of Hispanic and African American individuals[144]. The Alzheimer's Disease Sequencing Project–Follow-Up Study aims to increase the diversity of AD datasets through a specific focus on inclusion of individuals from a range of different ancestral populations[145]. By the end of 2023, approximately 40,000 whole genomes are expected to have been assembled and released for analysis.

Other efforts to improve the diversity of study populations in AD genetics research include the Research in African-American Alzheimer's Disease Initiative, which collates whole genomes from multiplex African American families, and the Recruitment and Retention for Alzheimer's Disease Diversity Genetic Cohorts[146], which will collect data from another 4,000 African American individuals and 4,000 Hispanic individuals as well as 5,000 individuals recruited from various sub-Saharan African countries. In addition, Estudio Familiar de Influencia Genetica en Alzheimer is conducting family-based AD genomic studies in Caribbean Hispanic populations, and a WGS study of Korean participants is being performed as part of the Gwangju Alzheimer's and Related Dementias (GARD) Study. Furthermore, studies are being performed in individuals of native Amerindian ancestry from the southern Peruvian Andes mountains, in Mexican individuals (Mexican Health and Aging Study), and in 2,000 Indian individuals from all parts of India (Longitudinal Aging Study in India). Finally, the Asian Cohort for Alzheimer's Disease is evaluating approximately 6,000 individuals of Chinese, Korean and Vietnamese ancestry with late-onset AD for genomic analyses. Several of these efforts also involve the acquisition of data on plasma or cerebrospinal fluid (CSF) biomarkers and multiomics. In addition, the ADNI4 study of the Alzheimer's Disease Neuroimaging Initiative[147] aims to enrol 50–60% of its new participants from populations previously under-represented in AD research studies in the USA by implementing improved culturally engaged approaches for recruitment and retention. We expect that these complementary efforts across populations of different ancestries will allow us to further disentangle the genetic contributions of individual ancestries to AD, identify genomic loci that are shared across ethnic groups, and pinpoint loci that are specific to a particular population. This would provide critical information on population-specific AD pathways, potential biomarkers, potential therapeutic targets for drug discovery, and observed health disparities.

Understanding phenotypic heterogeneity

Genetic studies require careful and thorough phenotyping. However, the criteria for the diagnosis of AD have evolved over the past few decades, resulting in somewhat of a moving target. The original diagnostic criteria for AD were created by a panel of experts from the National Institute of Neurological Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA) in 1984 (ref. 90). This committee categorized three diagnostic levels: definite AD (neuropathological diagnosis), probable AD (diagnosis without confounding factors), and possible AD (diagnosis with comorbidities). The sensitivity and specificity of the clinical criteria for probable AD compared with post-mortem diagnosis were 81% and 70%, respectively[148]. These criteria were revised in 2011 (ref. 148) to include pathophysiological changes. At this time, MRI, PET imaging and CSF analyte assays were just starting to be implemented in clinical and research settings, recognizing and reinforcing the observation that the underlying pathological changes related to AD can begin decades prior to the onset of clinical symptoms.

AD can be categorized into early-onset and late-onset forms on the basis of the age at which the first symptoms appeared. However, this classification can be arbitrary[149]: although the majority of genetic studies use a cut-off age of 65 years, some studies use 60 years of age[13,150]. Onset before age 65 years accounts for approximately 5–10% of AD[13,149],

corresponding to ~300,000–700,000 individuals in the USA. Both early-onset and late-onset groups present primarily with memory-predominant phenotypes; however, individuals with early-onset AD can have a more aggressive course of disease with a reduced survival time[151]. Approximately 25% of individuals with early-onset AD have an atypical clinical presentation characterized by language, visuospatial or executive dysfunction and preserved episodic memory[152]. Some have considered early-onset AD to represent the purest form of the disease, but this might not be the case. Individuals with the fully penetrant autosomal dominant early-onset form of AD can have an increased burden of white matter hyperintensities, which reflect microvascular pathology, compared with cognitively healthy non-carriers several decades older[153]. Regardless of the age at onset, extracellular Aβ plaques and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau protein are consistent at autopsy, and can be accompanied by cerebrovascular disease, Lewy bodies or other aggregated proteins[1]. TDP43 pathology, hippocampal sclerosis, vascular injury, pronounced brain atrophy[154], higher tau burden[155] and more widespread tau neuropathology have been associated with early-onset disease[156,157]. TDP43 deposition might even determine when hippocampal atrophy begins and the rate of neurofibrillary tangle accumulation[158].

At brain autopsy, 20% to 30% of individuals with clinically diagnosed AD had cerebrovascular disease or Lewy body pathology, and sometimes both, in addition to plaques and tangles[16,159–162] (Fig. 5). The results of neuroimaging and neuropathological studies indicate that cerebrovascular disease co-occurs with primary AD pathology and adds to disease manifestation[160,163]. Furthermore, a large body of epidemiological cohort studies has implicated a range of highly prevalent vascular risk factors including diabetes, insulin resistance, mid-life obesity and hypertension in dementia risk[164]. Whether cerebrovascular disease directly causes AD pathology or is a frequent comorbidity that contributes to the clinical phenotype remains an open question. Among individuals with AD, approximately 20% also have α-synuclein pathology, intraneuronal Lewy bodies and Lewy neurites[165–167]. The presence of Lewy body pathology in AD is associated with earlier symptom onset[168], worse cognition[169], faster progression[170] and parkinsonism[171]. Individuals with a high tangle load in the limbic system and cerebral neocortex are less likely to express the clinical features typical of dementia with Lewy bodies and tend to be diagnosed as having AD[172]. MRI studies further suggest that there are four atrophy pattern subtypes in AD: typical, limbic-predominant, hippocampal-sparing, and no atrophy[173]. The degree of clinical and neuropathological heterogeneity in AD can confound the functional understanding of genetics, making incorporation of additional information to improve diagnosis, such as blood-based biomarkers, critical. For example genetic influences in AD with associated cerebrovascular pathology, Lewy body accumulation or even TDP43 deposits have not been fully explored. Also, incorporating cerebrovascular disease and related risk factors in genetic studies of AD might provide novel information[174,175].

Improving diagnostic accuracy

The era of precision medicine has encouraged the development of refinements in the clinical diagnosis of AD, thereby improving phenotype–genotype analyses. The inclusion of MRI, PET and CSF assays in the 2011 research criteria for the diagnosis of AD[20] led

to a proposed research framework[176] that used biomarkers to create classifications that reflect the deposition of Aβ and tau proteins and neurodegeneration – the so-called A/T/N classification[177]. 'A' refers to evidence of Aβ accumulation in the brain provided by PET or low CSF $A\beta_{1–42}$ concentration. 'T' refers to tau pathology indexed with PET or increased tau concentration in CSF. 'N' refers to neurodegeneration and would be reflected by regional atrophy on MRI. As discussed in the preceding section, individuals with a clinical diagnosis of AD can have a range of underlying pathological changes, which can begin decades before diagnosis. Therefore, incorporating biomarker assessment into genetic studies might enable more accurate diagnoses and the identification of asymptomatic individuals with causal variants.

PET and CSF biomarkers have excellent sensitivity and specificity for AD and have been compared across countries, which identified variation across laboratories and led to efforts to standardize and harmonize these assays[178]. These biomarkers have also been used in genetic studies in several highly resourced countries in North America, Europe and Asia (Box 2). Interestingly, *APOE* ε4 was associated with increased brain Aβ deposition as measured using ^{11}C-labelled Pittsburgh compound B and ^{18}F-florbetapir PET in two relatively small studies in the USA and China[179,180]. In the study in the USA, SNPs from 20 genes previously associated with AD were analysed and Aβ deposition was found to be associated with variants in *ABCA7* and *FERMT2*. In the largest of these studies to date, *RBFOX1*, a neuronal RNA binding protein, was found to be associated with brain amyloidosis in a cohort of >4,000 individuals in the USA[181].

Several groups have investigated genetic associations with CSF biomarker levels in individuals with AD. CSF concentrations of $A\beta_{1–42}$, t-tau, and p-tau181 were associated with four variants in the *APOE* region[182], and CSF p-tau concentrations were higher in participants carrying *APOE* ε4 than in those with other *APOE* alleles[182]. In studies with larger sample sizes, additional loci associated with the same CSF biomarkers were uncovered on 3q28 and 6p21.1, near the *TREM2* gene cluster[183] and 1p32.2 and 6p25 were found to be associated with AD risk, progression and age at onset[184]. In another study, variants in the *MS4A4A* gene were associated with increased CSF concentrations of TREM2 and reduced AD risk, indicating that the *MS4A* gene cluster is a key modulator of soluble TREM2 and AD risk[185]. Variants in *AMTS1, TMEM106B* and *CPOX* have been associated with CSF levels of neurofilament light chain (NfL) in individuals with AD[34,186]. In a small Chinese cohort, variants in several genes known to be associated with AD were found to also be associated with CSF levels of $A\beta_{1–42}$, $A\beta_{1–42}$ to $A\beta_{1–40}$ ratio, t-tau and p-tau181 (ref. 187).

In addition to the detection of neurodegeneration as part of the A/T/N framework, structural imaging using MRI and diffusion tensor imaging can detect other changes in the brain (such as white matter hyperintensities) that are associated with AD and cognitive dysfunction, but lack sufficient sensitivity or specificity to be considered as biomarkers. There are several studies indicating that these findings can be genetically determined[188,189]. *APOE* ε4 and several single nucleotide variants in additional genes previously associated with AD in large genome-wide array studies have been found to be associated with structural changes on MRI[190–192]. In a Korean cohort, a missense variant

in *SHARPIN* was found to be associated with measures of atrophy as manifested by loss of hippocampal volume and entorhinal cortical thickness, especially among individuals with AD[193]. Another investigation combined genome-wide array data, information on structural changes from MRI and cognitive measures in individuals with AD, and identified novel loci in or near *EHBP1, CEP112, SMOC2* and *IL1RAPL1* that were associated with cognitive phenotypes[190].

Blood-based biomarkers.—Evidence indicates that recently developed blood-based biomarkers[194,195] can strengthen the diagnoses of AD, mild cognitive impairment and cognitive decline, and allow prediction of incident disease. Blood-based biomarkers provide an unparalleled opportunity to incorporate biomarker information in practice worldwide including low-resourced countries where brain imaging and CSF analysis might not be possible. In a genetic association study performed in the UK that included individuals with AD and cognitively healthy controls and was adjusted for age, sex, population stratification and case–control status, the presence of an *APOE* ε4 allele was associated with levels of all blood-based biomarkers, including $A\beta_{1–40}$, $A\beta_{1–42}$, glial fibrillary protein and NfL[196] A GWAS from the Alzheimer's Disease Neuroimaging Initiative found three variants in *CD1A* that were associated with blood NfL levels in individuals without dementia (mean age 72.9 years)[197]. In individuals with AD and healthy controls from China, total AD polygenic risk score was associated with plasma concentrations of $A\beta_{1–42}$, t-tau and NfL, and $A\beta_{1–42}$ to $A\beta_{1–40}$ ratio[198]. Gene-based analyses of the data in this study indicated that *ABCA7* and *UNC5C*, as well as *APOE* ε4, were the main contributors to the association.

A worldwide approach by the Alzheimer's Disease Neuroimaging Initiative is a collaborative effort to investigate imaging and biofluid markers for AD across North America, Europe, Argentina, Australia, China,Japan, Korea, Mexico and Taiwan. Collaboration among these developed countries will improve precision in the diagnosis of AD and related disorders. However, biomarker-based studies of populations in low-income countries, which, according to the WHO, includes 58% of people in the world with dementia, remain scarce. Therefore, the inclusion of readily available, blood-based biomarkers in genetic studies would greatly augment phenotype characterization worldwide.

Functional genomics

Investigators have initiated functional studies that use approaches such as epigenomics, transcriptomics, proteomics and metabolomics to better understand the genetic bases of familial and sporadic AD and related disorders (Box 3). Integrated multiomics approaches can be driven by the phenotype, the environment or the genome. The phenotype approach uses multiomics layers to compare individuals with a disease with healthy controls and can define more homogeneous subgroups than clinical diagnosis alone. These subgroups can have unique genetic profiles. The environmental approach uses multiomics analyses to investigate mechanistic links to environmental or medical risk factors such as vascular disease, physical activity, smoking and sleep. The genome approach is a variant-centred or gene-centred integration of harmonized multiomics to determine causality and identify underlying mechanisms.

Investigating AD-associated genetic variants as quantitative trait loci (QTL) for epigenomic, transcriptomic, proteomic and metabolomic variables can be used to explore how variants in genes perturb pathways leading to AD. Multiomics approaches can also be used to validate variants of uncertain significance. Additionally, associations between genetic variants and exogenous metabolites allow assessment of gene–environment interactions in AD. Non-coding RNAs (ncRNAs) – including long ncRNAs, circular RNAs, small non-coding microRNAs and natural antisense transcripts – have been shown to regulate signalling pathways involved in AD (such as apoptosis, mitochondrial dysfunction and neurotrophic factor depletion in neurons and microglia)[199]. The role of ncRNAs can be investigated with transcriptomic and epigenetic approaches but to date the specific set of ncRNAs involved in AD has yet to be identified.

The genes that have been consistently associated with AD have shaped approaches to elucidating the causes of AD, and might yet reveal potential targets for therapeutic development; however, the existing multiomics data have some limitations. First, despite the identification of many AD-associated loci, the downstream effects of only a fraction have been studied. Second, the possibility that AD might result from changes in the regulation of gene expression by ncRNAs has not been fully explored[200,201]. Third, many previous multiomics studies have focused on post-mortem tissues, which generally represent the end stage of AD, so the identified associations could reflect disease progression and not disease risk. Fourth, large multiomics datasets have been collected from non-Hispanic white individuals but few such datasets exist for other ethnic and racial groups, hindering comparisons.

Multiomics approaches offer an opportunity to understand the ‘flow of information’ that underlies disease (Fig. 6). AD is by its very nature a non-linear, genetically driven, pathophysiological disease with high heterogeneity in biological alterations[202]. Failure of multilevel biological systems underlying AD includes proteostasis (Aβ and tau), synaptic homeostasis, inflammatory and immune responses, lipid and energy metabolism, and oxidative stress. The various ‘omics’ do not exist in isolation, but are part of a poorly understood and highly complex and interdependent system[203,204]. Therefore, a systems-level understanding of AD, with generation of robust multiomics datasets across diverse ancestries and harmonization of the results to include associated genes, is needed to understand underlying disease mechanisms and to inform our understanding of the biological continuum of this disease.

Conclusions

If we are to fully understand the genetic influences on the common biology of AD, it is crucial that we identify the broadest range of genetic variations that influence AD. Expansion of ongoing efforts to sequence and analyse the genomes in under-sampled areas of the world, ideally combined with acquisition of additional multiomics data and appropriate development of infrastructure, resources, training and ethical guidelines to support this research, will be essential to improve our understanding of global genetic variation profiles and disease. To achieve this aim, a wide range of barriers to research participation will need to be addressed to improve inclusion of under-represented population

groups. It will also be essential to address the shortage of biomedical research infrastructure and expertise, expand support for the integration of international collaborative efforts and increase community engagement to broaden the cultural acceptability of biobanking and genomic research. A WGS study of individuals from over 50 ethnolinguistic groups by the Human Health and Heredity in Africa (H3Africa) consortium that was published in 2020 aimed to further characterize African genomic diversity (that is, the region with the greatest level of human genetic variation)[205]. This effort identified more than three million previously undescribed genetic variants, and refined our understanding of patterns of ancestral admixture, continental migration, gene flow and the response to human disease[205], underscoring the scientific imperative for a broader characterization of the global genomic diversity to develop treatments that will be effective for everyone.

To improve precision in genetic studies and the diagnosis of AD in clinical and research settings, it will be crucial to obtain and validate biomarker information in low-income countries across the world. Standardizing and harmonizing a range of phenotypes using imaging and fluid biomarkers would improve the phenotype–genotype analyses of populations across the world. Ultimately, such an endeavour would allow investigators to develop a precision medicine approach, which might differ across ancestral groups. The limited availability of PET facilities and laboratories equipped to analyse biomarkers in some countries underscores the urgent need to develop improved biomarkers that are inexpensive and readily available to all.

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Related links

Alzheimer's Disease Neuroimaging Initiative: https://adni.loni.usc.edu/

Alzheimer's Disease Sequencing Project-Follow-Up Study (ADSP-FUS): https://adsp.niagads.org/

Alzheimer's Disease Sequencing Project-Follow-Up Study: https://www.nia.nih.gov/research/ad-genetics

Asian Cohort for Alzheimer's Disease: https://acadstudy.org/

Estudio Familiar de Influencia Genetica en Alzheimer (Puerto Rican Alzheimer Disease Initiative; EFIGA): https://dss.niagads.org/cohorts/estudio-familiar-de-influencia-genetica-en-alzheimer-efiga/

Gwangju Alzheimer's and Related Dementias (GARD) Study: https://dss.niagads.org/cohorts/gwangju-alzheimers-and-related-dementia-gard/

Longitudinal Aging Study in India: https://lasi-india.org/

Mexican Health and Aging Study: https://www.mhasweb.org/Home/index.aspx

Research in African American Alzheimer's Disease Initiative (REAAADI): https://med.miami.edu/centers-and-institutes/hihg/research-programs/alzheimers-disease-and-related-dementias/research-in-african-american-alzheimer-disease-initiative

WHO dementia fact sheet: https://www.who.int/news-room/fact-sheets/detail/dementia

Glossary

Kindred
An aggregate of genetically related individuals.

Principal components
Principal components analysis is a statistical method commonly used in population genetics to identify substructure in the distribution of genetic variation within populations.

Quantitative trait loci
Regions of DNA each associated with a particular quantitative phenotypic trait.

Recombination
Genetic recombination is the exchange of genetic material between different individuals which leads to offspring with combinations of traits that differ from those in either parent.

Variants of uncertain significance
Genetic variants for which association with a specific trait is unclear.

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Key points

- The genetic variation underlying Alzheimer disease (AD) differs across ethnic groups.
- Large-scale genomic studies have identified over 70 genes or genetic loci associated with AD risk, but these data have largely been obtained from populations in Europe and North America, which hinders our understanding of the molecular mechanism(s) underlying the disease in under-represented populations and the development of a personalized therapeutic approach.
- Expansion of efforts to sequence and analyse the genomes of people from under-studied areas of the world, combined with acquisition of additional multiomics data and appropriate development of infrastructure, resources, training and ethical guidelines, will be essential to improve our understanding of global genetic variation profiles underlying dementia.
- Pathological heterogeneity is the norm in AD and efforts to incorporate this information into genetic studies is underway.
- Incorporation of improved biomarkers that can be obtained in low-resource countries will be critical to increase diagnostic accuracy in these efforts.

Box 1

Types of genetic study

Family-based studies

Family-based studies have been used for decades to investigate many monogenic disorders. Investigation of multigenerational families facilitated the discovery of presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*) and amyloid precursor protein (*APP*) in early-onset, autosomal dominant Alzheimer disease (AD). However, families with late-onset AD have also been widely recruited and used in linkage and family-based association studies [209–212]. Family-based studies are most feasible when onset of the disorder is at a young age, so that the proband's parents are still alive[213,214]. Challenges to this type of analysis include the variable age at onset and penetrance of disease as well as the clinical and genetic heterogeneity of AD, even within a family.

Case–control studies

The case–control design is the most frequent approach used now to identify genetic variants contributing to disease owing to the relative ease in recruiting individuals. This design seeks to identify differences in allele or genotype frequencies between a group of participants with AD and a group of healthy controls. This approach was used to identify the apolipoprotein E association with AD. However, participants in the two groups must be rigorously defined and matched for key factors such as ancestry. Observational studies with a mix of individuals with AD and healthy individuals can also estimate the effect of a variety of genetic and other risk factors on outcomes and can also contribute to our understanding of novel genetic risk factors. Thus, longitudinal, observational studies such as the Alzheimer's Disease Neuroimaging Initiative can provide a broad assessment to evaluate a wide range of biomarkers and outcomes.

Observational cohort studies

Observational cohort design can also be used to examine the effect of risk factors in a population-based setting in which the number of cases reflects the population incidence rate. The Washington Heights–Inwood Columbia Aging Project is a multi-ethnic cohort consisting of African Americans, non-Hispanic white individuals, and Caribbean Hispanic individuals all recruited from northern Manhattan[47]. Another well-known longitudinal prospective cohort is the Adult Changes in Thought study that randomly recruited individuals 65 years of age or older, living in Seattle, who were members of Group Health and were cognitively intact at the time of enrolment in Adult Changes in Thought[215]. A limitation of this approach can be the clinical and genetic heterogeneity within the cohort, which can confound the results.

Box 2

Biomarkers for Alzheimer disease

Brain MRI

Alzheimer disease (AD) is accompanied by neurodegenerative changes that are detectable with structural MRI years before the clinical diagnosis[216]. Neurodegeneration presents as patterns of cortical thinning[217] and focal atrophy in the medial temporal lobe[218]. Structural MRI captures cerebral comorbidities in AD, including ischaemic lesions and haemorrhagic lesions.

Amyloid and tau PET imaging

PET is another neuroimaging tool, and the development of molecularly based amyloid and tau tracers has greatly changed the ability of PET imaging to enhance the diagnosis of AD. The need for obtaining and storing radioactive biomarkers, the expense of acquiring the images and the feasibility of imaging large numbers of individuals have prevented the use of PET in individuals with AD in routine clinical settings.

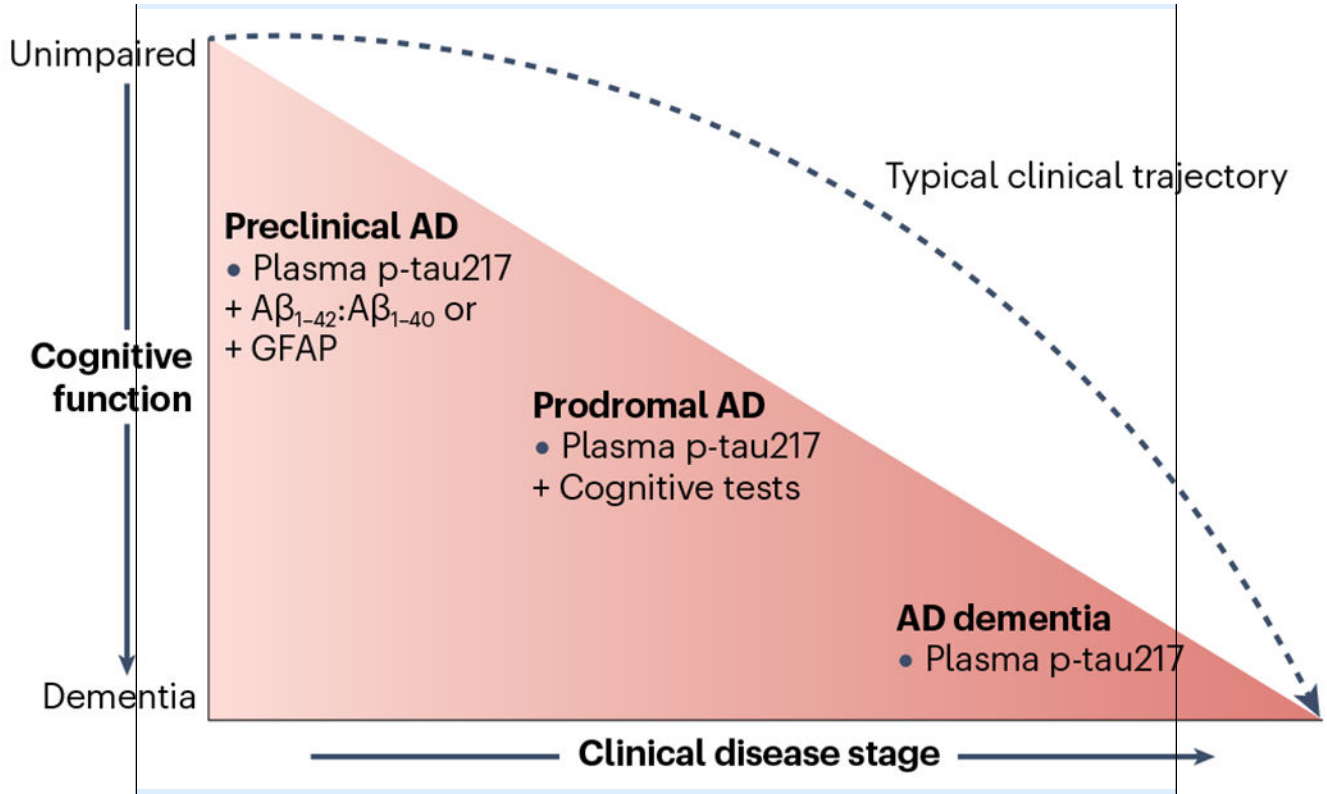
Cerebrospinal fluid biomarkers

Biomarkers in the cerebrospinal fluid (CSF) including amyloid-β ($A\beta_{1–42}$), total tau (t-tau), and tau phosphorylated at threonine 181 or 217 (p-tau) reflect the underlying pathophysiology of AD and can aid in the differential diagnosis. A recent worldwide multicentre harmonization project generated consensus interpretations of CSF biomarkers in AD[219]. Some evidence suggests that CSF biomarkers, particularly measures of t-tau and p-tau, can differ between individuals of African ancestry and non-Hispanic white individuals[220,221].

Blood-based biomarkers

Technological advances have now made it possible to measure AD biomarkers in plasma[222] (see the figure) — single-molecule array-based assays are now available for $A\beta_{1–42}$, p-tau181 and p-tau217 (ref. 223). Plasma concentrations of neurofilament light chain (NfL), a marker of neuronal injury, are increased in AD and provide a sensitive biomarker for neurodegeneration[224,225]. Plasma NfL concentrations are associated with neurofibrillary tangle pathology and neurodegeneration measured at autopsy[226].

Research into AD biomarkers across racial and ethnic groups has been challenged by small sample sizes, difficulty recruiting participants and selection biases. More work and greater collaboration are required on a global scale.



Most promising blood-based biomarkers for AD by disease stage.
Adapted from ref. 222, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

Box 3

Functional genomics

Epigenetics

Epigenetics represents a dynamic molecular modification that influences gene expression and can be sensitive to genetic variation, environmental factors and disease state[227]. Altered DNA methylation is involved in Alzheimer disease (AD) and affects gene expression[228]. CpG-related single-nucleotide polymorphisms (CGS) alter the sequence of the primary target sites for DNA methylation[229] and account for a substantial fraction of allele-specific methylation in the human genome [230,231]. More than 80% of CGS have a regulatory role in DNA methylation [232]. Epigenome-wide association studies can identify disease-associated methylomic variation.

Transcriptomics

Transcriptomics measures the amounts of transcripts (both mRNA and non-coding RNA (microRNAs, long non-coding RNAs and circular RNAs)) being made, can be used to identify novel genetic associations, and can explain associations between gene expression, disease and genetic variants. Transcriptome sequencing has been used in conjunction with whole-exome and whole-genome sequencing, and multiple types of RNA transcripts have been associated with AD in post-mortem brain [107,233].

Proteomics

Proteomics analyses involve the identification and quantification of proteins present in tissues and biological fluids. Proteins are effectors of biological function, and their levels are not only dependent on corresponding messenger RNA levels but also on host translational control and regulation. Second to genetic mapping, proteomic investigations can validate disease pathways and uncover novel protein networks and mechanisms, such as RNA splicing, development, immunity, membrane transport, lipid metabolism, synaptic function and mitochondrial activity.

Metabolomics

Metabolite levels can be associated with disease or with related underlying biological mechanisms [234], and are influenced by the environment, medications, diet, alcohol and tobacco use, sex[235], ethnic group [236–239] and genetic variation [238,240]. A comprehensive assessment of exogenous, endogenous and microorganism-derived metabolites can reflect both the environmental exposures and the biological response[241]. Plasma is a readily available source for metabolomics analysis, and studies using this approach can augment the functional assessment of genetic variants in AD.

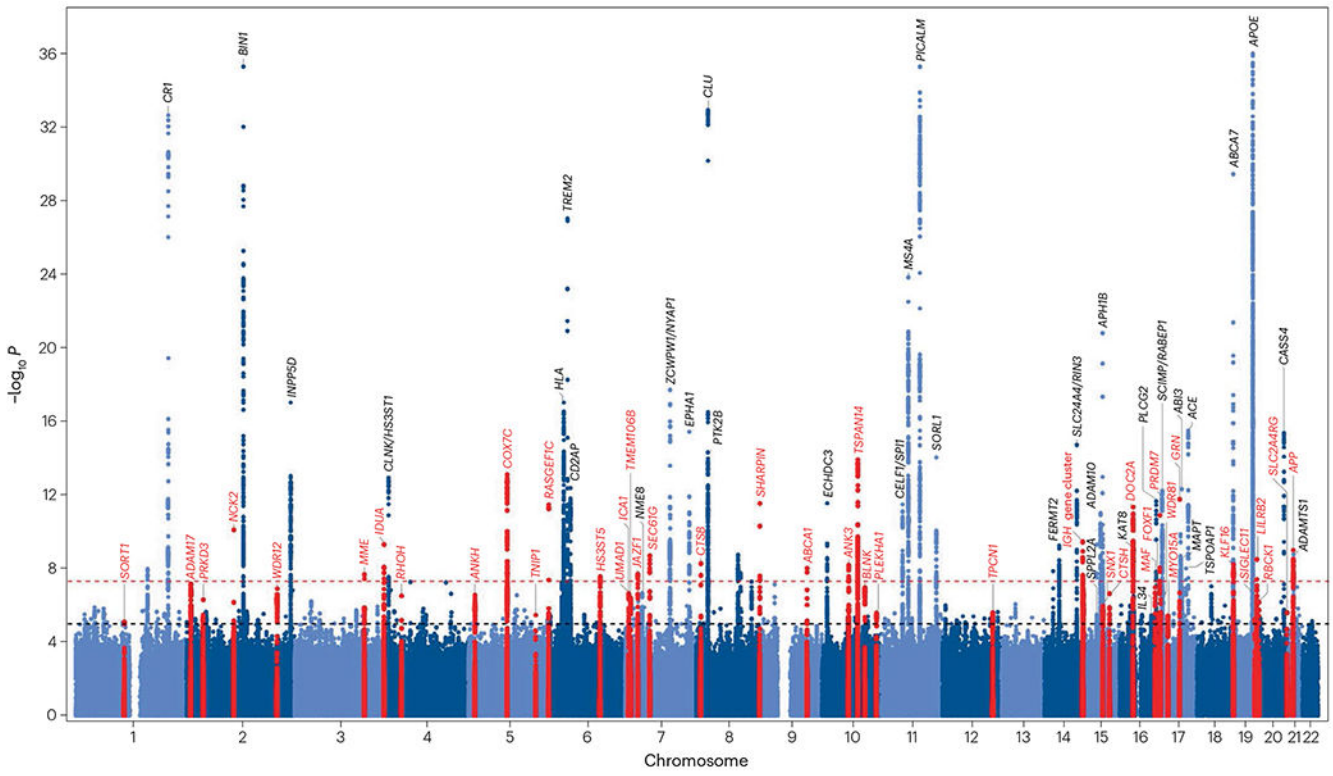


Fig. 1 |. Genetic loci associated with Alzheimer disease in genome-wide association studies of non-Hispanic white individuals.

Manhattan plot from a study by Bellenguez and colleagues[16] showing the identified genetic loci associated with Alzheimer disease in non-Hispanic white individuals. *P* values are two-sided raw *P* values derived from fixed-effect meta-analysis. The threshold for genome-wide significance ($P = 5 \times 10^{-8}$) is indicated by the red dashed line, and the suggestive threshold for genome-wide significance ($P = 1 < 10^{-5}$) is indicated by the black dashed line. Loci are named for the closest gene to the sentinel variant for each locus. Loci newly identified by Bellenguez et al. are shown in red, whereas loci previously reported are shown in light and dark blue. Adapted from ref. 16, Springer Nature Limited.

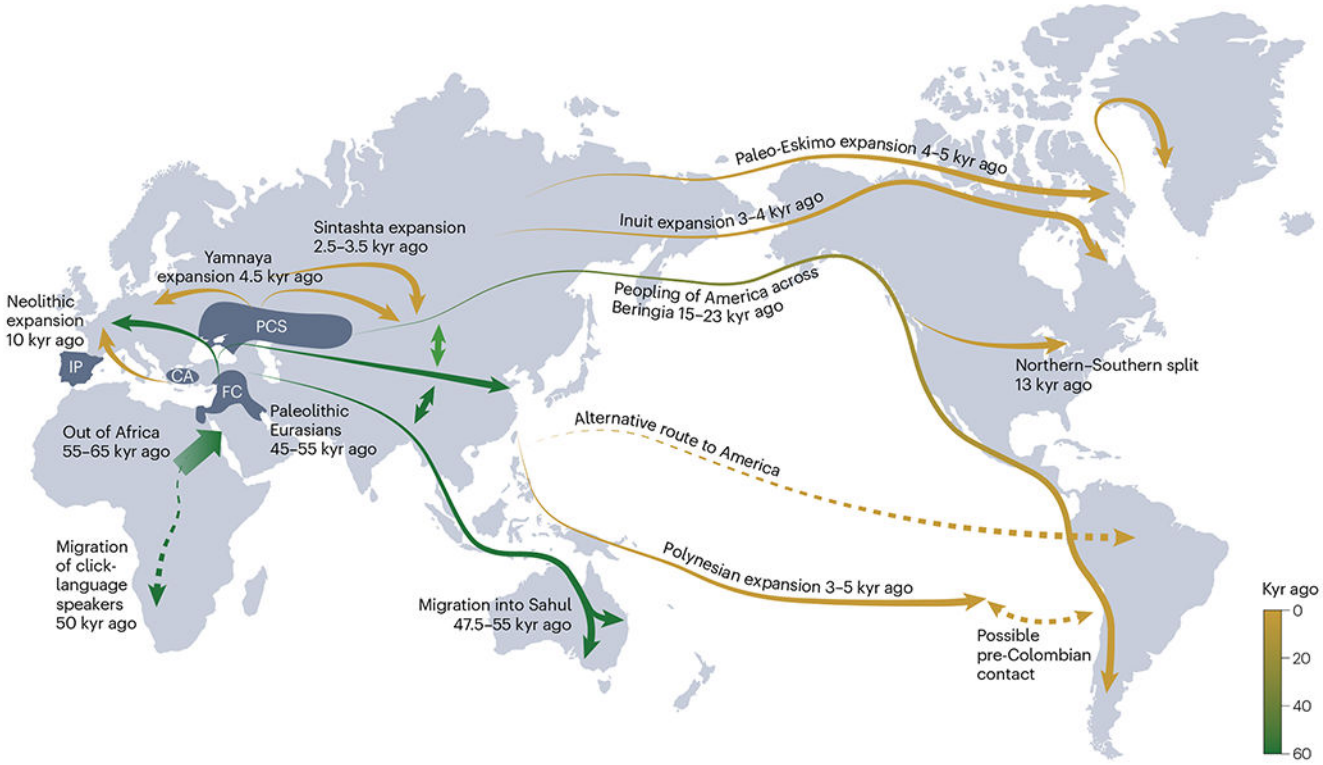


Fig. 2 |. Timeline and routes of human migration inferred from genomic data.

Dashed lines represent routes of migration that remain controversial. CA, Central Anatolia; FC, Fertile Crescent; IP, Iberian Peninsula; kyr, thousand years; PCS, Pontic-Caspian steppe. Adapted from ref. 208, Springer Nature Limited.

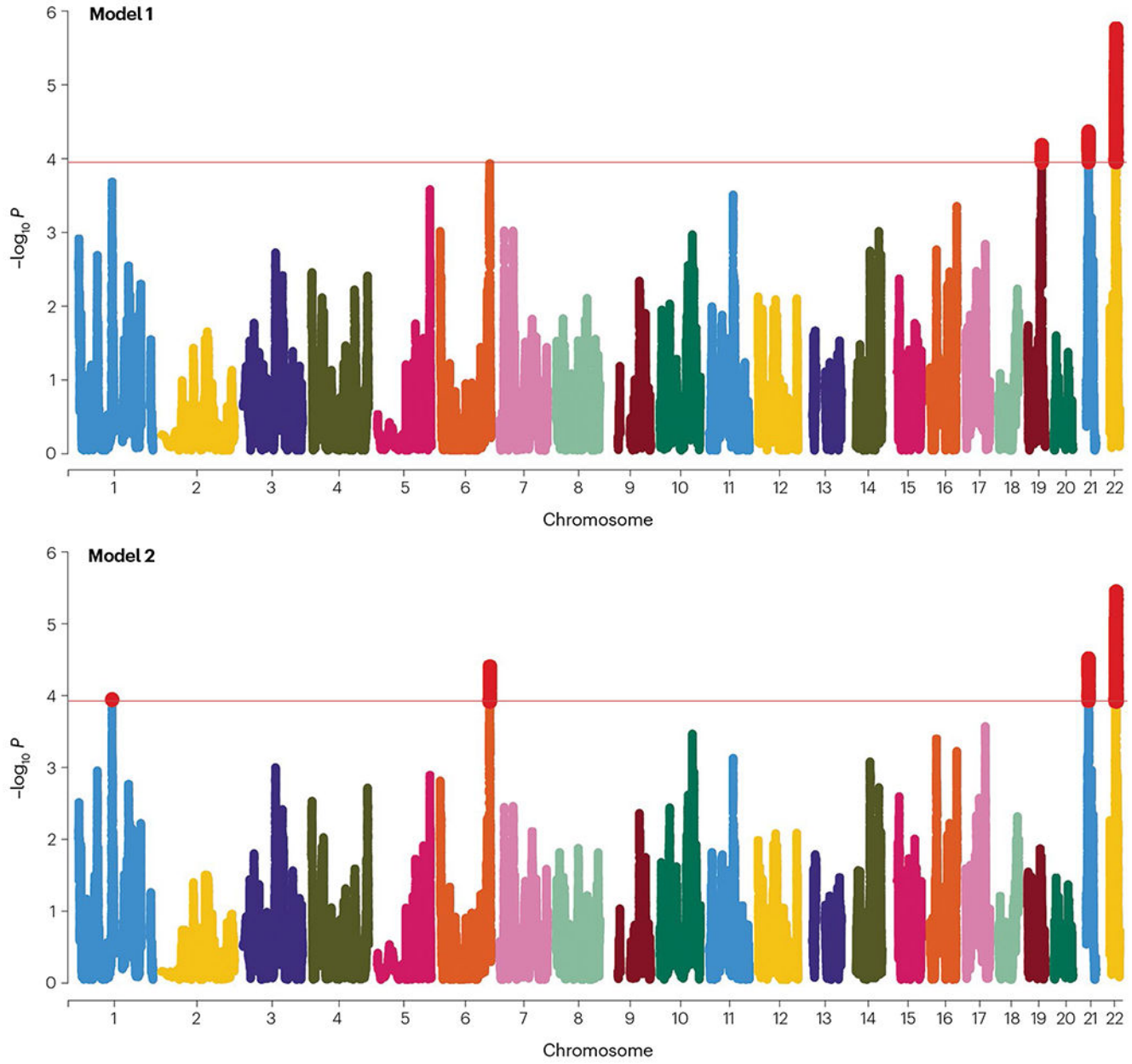


Fig. 3 |. Admixture mapping of Alzheimer disease in Caribbean Hispanic individuals.
Manhattan plots of analyses conducted in admixMap. Model 1 (upper panel) is adjusted for age, sex, genotype batch, principal components for population stratification, and kinship. Model 2 (lower panel) is in addition adjusted for *APOE* genotype. The red highlighted parts represent the identified ancestral blocks significant after multiple testing correction. Adapted from ref. 109, Springer Nature Limited.

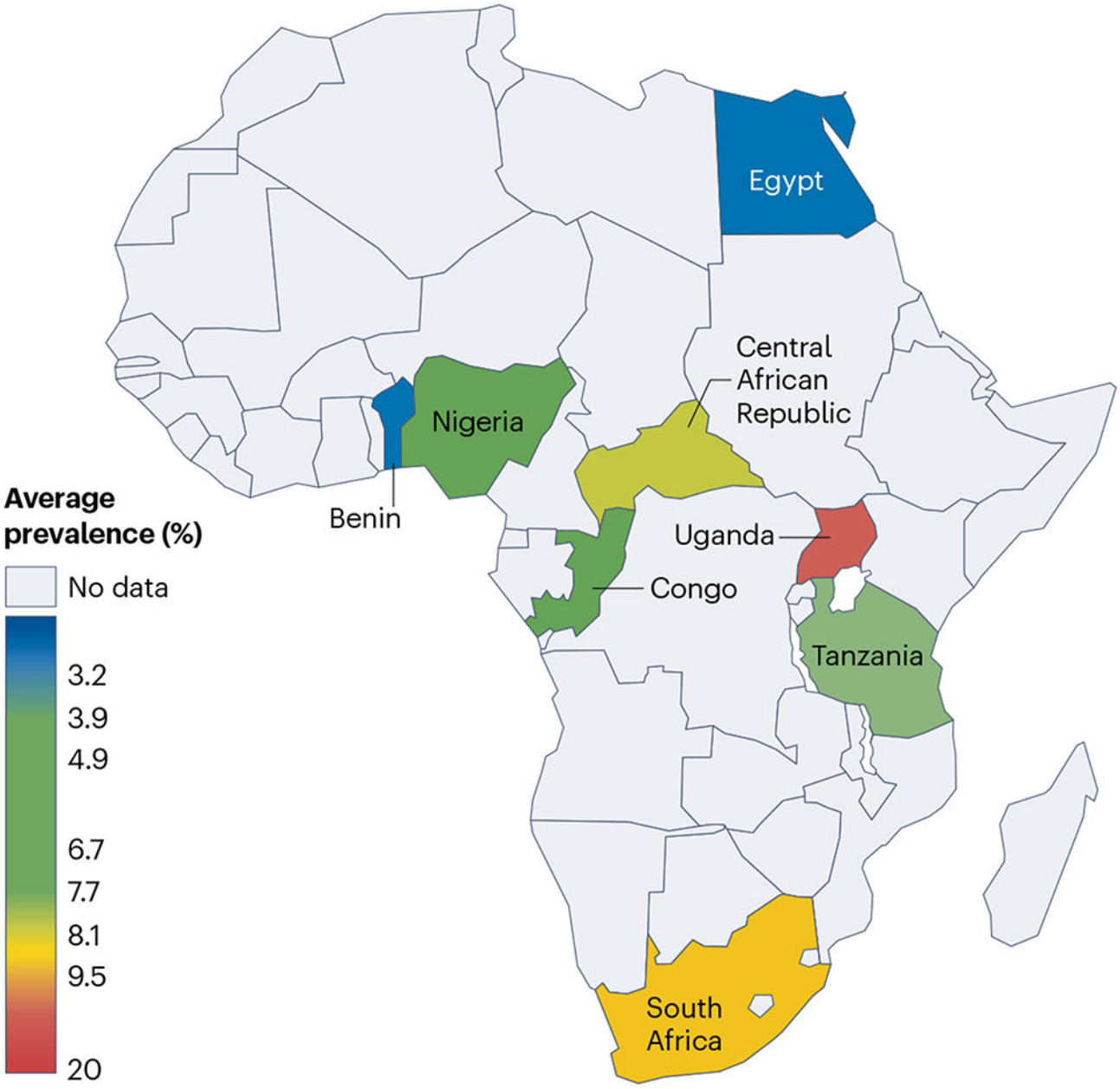


Fig. 4 |. Prevalence of dementia in Africa.

Heat map showing the wide range of dementia prevalence in African countries determined over the past 25 years. Dementia prevalence studies have also been conducted in Senegal and Kenya, but the data are not yet published. Adapted with permission from ref. 143, Wiley.

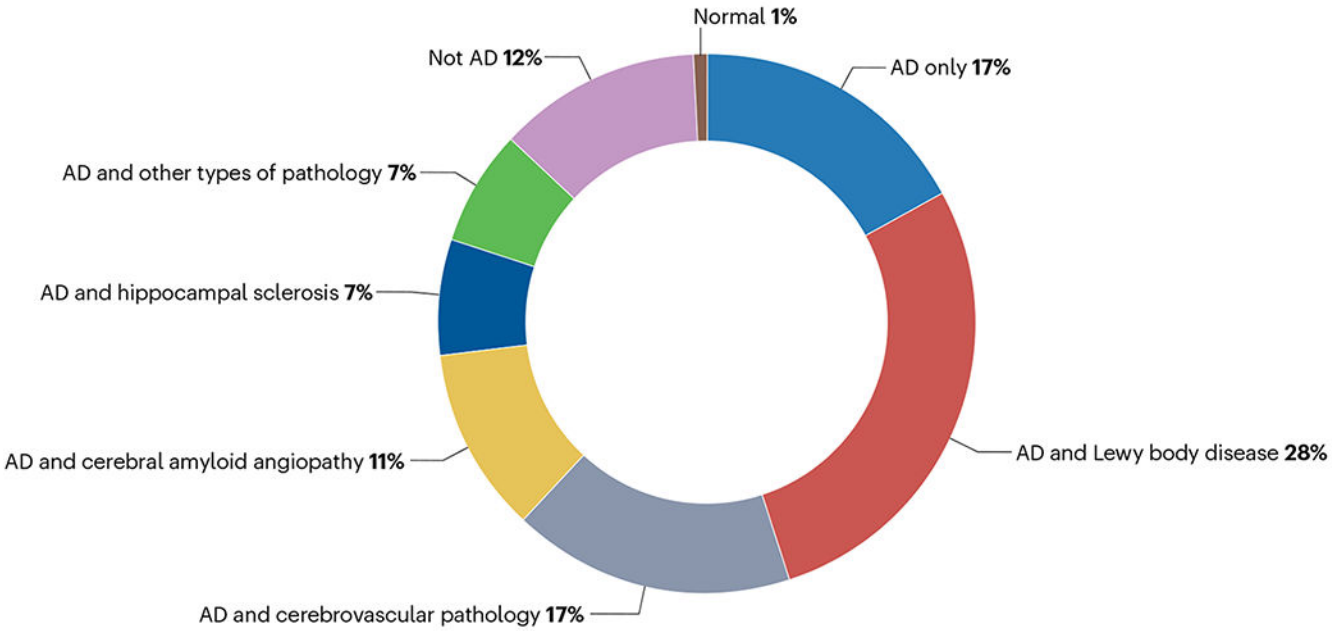


Fig. 5 |. Pathology in clinically diagnosed Alzheimer disease.

The proportions of other types of pathological changes in individuals with clinically diagnosed Alzheimer disease (AD). The data are from a publication by DeTure and Dickson[162], in which they describe the pathological evaluation of 626 individuals from the Mayo Clinic Brain Bank. ‘Not AD’ indicates a completely distinct form of dementia.

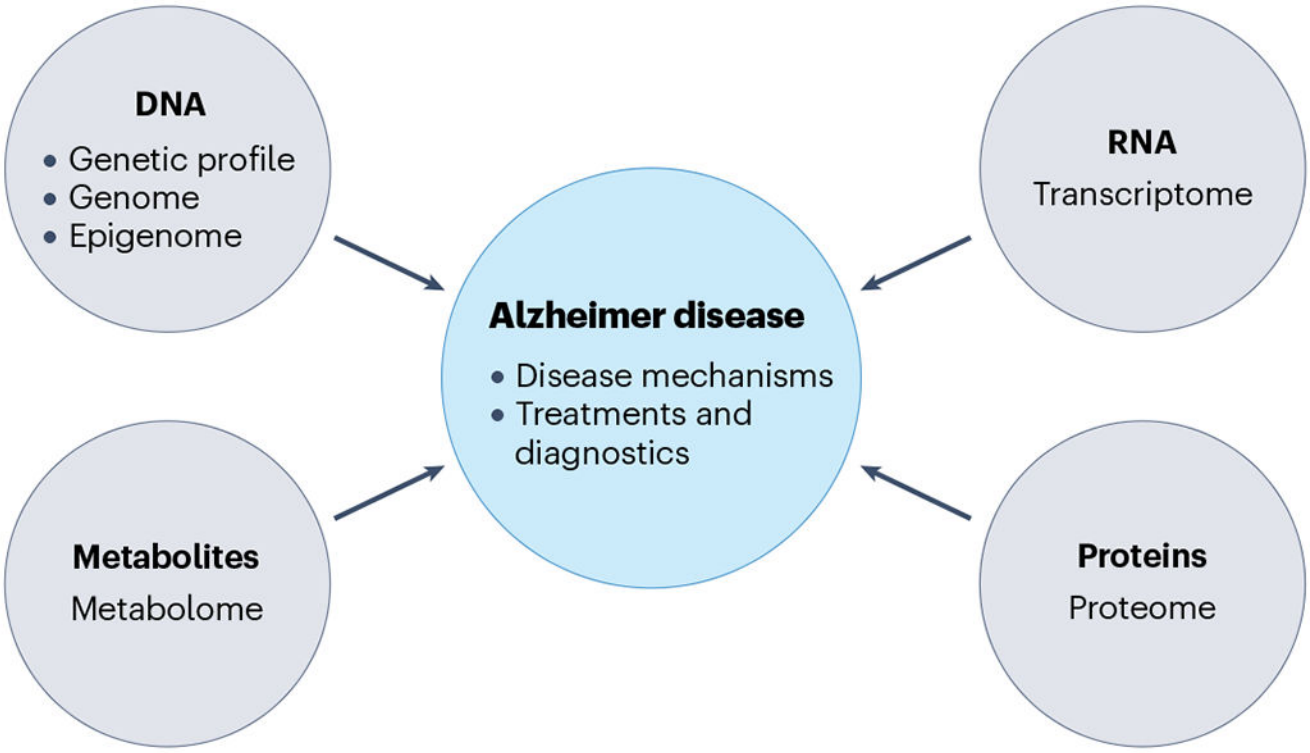


Fig. 6 |. An integrated multiomics approach.

Integrated multiomics approaches can be used to understand how genetic variation leads to disease, to establish which molecular pathways are altered, and to identify new therapeutic targets and diagnostic approaches. Expression quantitative trait loci (eQTLs) would be generated from each omics layer (gene expression from the transcriptome, protein quantitative traits from the proteome, methylation quantitative traits from the metabolome). These multiomics layers would then be integrated into a systems analysis that includes information on the genome and epigenome, with the goal of furthering understanding of disease mechanisms and developing novel treatments and diagnostics.

Table 1 |

Genetic loci with a *P* value of $\leq 10^{-7}$ identified in GWAS of AD in African Americans

SNP	Position (hg38)	Closest gene	Minor allele	MAF	Ref.
rs115684722	1:23,224,0417	*SIPA1L2*	T	0.003	36
rs2633682	3:104,690,364	*ALCAM*	A	0.338	36
rs168193	3:5,260,392	*EDEM1*	G	0.267	36
rs145848414	5:174,587,111	*NSG2/MSX2*	A	0.0416	38
rs184179037	5:37,483,838	*WDR70*	T	0.0008	36
rs7748513	6:41,160,234	*TREM2* [a]	A	0.459	36
rs112404845	7:51,510,325	*COBL*	T	0.01	206
rs569584007	11:43,145,292	*API5* [b]	G	0.0023	36
rs115816806	11:76,830,796	*ACER3*	G	0.0083	36
rs75739461	12:18,318,612	*PIK3C2G*	A	0.0151	36
rs9516245	13:93,507,547	*GPC6*	C	0.0189	36
rs570487962	15:97,449,455	*ARRDC4/IGF1R*	C	0.0008	36
rs79537509	16:8,238,399	*RBFOX1* [a]	A	0.007	36
rs115550680	19:1,050,421	*ABCA7* [a]	G	0.0681	38
rs157591	19:44,920,677	*APOE* [a]	A	0.1422	38
rs3745495	19:50,021,075	*VRK3* [c]	G	0.0877	36

A *P* value cut-off of $\leq 10^{-7}$ indicates loci suggestive of genome-wide significance. GWAS, genome-wide association study; hg38, Genome Reference Consortium Human Build 38; MAF, minor allele frequency; SNP, single-nucleotide polymorphism.

[a] Locus is also observed in non-Hispanic white individuals.

[b] 5 Mb apart from but not in linkage disequilibrium with *CELF1/SPI1* locus observed in non-Hispanic white individuals[16].

[c] 1.7 Mb apart from but not in linkage disequilibrium with *CD33* observed in non-Hispanic white individuals[17].

Table 2 |

Genetic loci reported with a *P* value of ≤10^{-5} by GWAS or WGS studies in East Asian populations

SNP	Position (hg38)	Closest gene	Minor allele	MAF	Ref.
Japan					
rs4598682	11:121505242	*SORL1* [a]	G	0.192	207
rs1992269	18:1872316	*ENSG00000266602*	T	0.018	116
rs802571	7:146265094	*CNTNAP2* [a,b]	G	0.029	
rs11613092	12:118455443	*SUDS3*	T	0.1367	
rs920608	4:76217307	*FAM47E/SCARB2*	C	0.044	120
China					
rs72713460	14:54830325	*GCH1*	T	0.134	121
rs2591054	15:57320212	*LINC01413*	T	0.246	
rs73052335	19:44916825	*APOC1/APOE*	C	0.092	
rs928771	21:38291838	*KCNJ15*	G	0.154	117
rs3777215	5:95786296	*RHOBTB3/GLRX*	A	0.168	
rs6859823	5:106218683	*ENSG00000252337*	T	0.369	
rs234434	14:97354683	*LINC02325*	G	0.237	
rs2255835	21:18119346	*CHODL*	C	0.321	
South Korea					
rs1890078	10:107218478	*SORCS1*	C	0.064	119
rs12594991	15:92973197	*CHD2*	A	0.141	
rs189753894	19:13513675	*CACNA1A*	A	0.359	
rs2280575	3:66492439	*LRIG1*	G	0.059	

A *P* value cut-off of ≤10^{-5} indicates loci suggestive of genome-wide significance. GWAS, genome-wide association study; hg38, Genome Reference Consortium Human Reference[37]; MAF, minor allele frequency; SNP, single nucleotide polymorphism; WGS, whole-genome sequencing.

[a] Locus is also observed in non-Hispanic white individuals.

[b] Variants in *CNTNAP2* have also been reported to be associated with vascular dementia in individuals from Spain[174].