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Genetic architecture of Alzheimer's disease

Sarah M. Neuner[a,1], **Julia TCW**[a,1], **Alison M. Goate**[a,b,*]

[a]Nash Department of Neuroscience, Ronald M. Loeb Center for Alzheimer's Disease, Icahn School of Medicine at Mount Sinai, New York, U.S.A

[b]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, U.S.A

Abstract

Advances in genetic and genomic technologies over the last thirty years have greatly enhanced our knowledge concerning the genetic architecture of Alzheimer's disease (AD). Several genes including *APP*, *PSEN1*, *PSEN2*, and *APOE* have been shown to exhibit large effects on disease susceptibility, with the remaining risk loci having much smaller effects on AD risk. Notably, common genetic variants impacting AD are not randomly distributed across the genome. Instead, these variants are enriched within regulatory elements active in human myeloid cells, and to a lesser extent liver cells, implicating these cell and tissue types as critical to disease etiology. Integrative approaches are emerging as highly effective for identifying the specific target genes through which AD risk variants act and will likely yield important insights related to potential therapeutic targets in the coming years. In the future, additional consideration of sex- and ethnicity-specific contributions to risk as well as the contribution of complex gene-gene and gene-environment interactions will likely be necessary to further improve our understanding of AD genetic architecture.

1. Introduction to Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia in the elderly [1]. Dementia, caused by a variety of disorders, is clinically characterized by a deterioration in memory, learning, spatial orientation, language, comprehension, and judgement severe enough to interfere with daily living [2]. AD usually presents with deficits in short-term memory formation and disturbance of additional cognitive functions including word-finding, spatial orientation, reasoning, judgement, and problem-solving [3, 4]. Of all dementia patients, 70% are diagnosed with AD, which approximates to 44 million individuals worldwide as of 2019 [2]. As age is one of the most

*Corresponding author : alison.goate@mssm.edu.

[1]Authors contributed equally

9. Author Contributions

SMN, JTCW, and AMG wrote the manuscript. SMN and JTCW generated the table and the figure. All authors discussed and reviewed the manuscript.

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significant risk factors for the disease, this number is expected to increase dramatically in the coming years due to the growing population of aged individuals. Given there is still no cure for disease, this presents a major public health concern.

In addition to clinical symptoms, AD is characterized by specific pathological features [5]. First described by Alois Alzheimer in 1906 [6], AD is a neurodegenerative disease defined by the presence of extracellular plaques primarily composed of beta-amyloid (Aβ) protein, a byproduct of sequential cleavage of the amyloid precursor protein (*APP*) by the enzymatic complexes beta (β) and gamma (γ) secretase [7, 8]. Intracellular aggregates composed of hyperphosphorylated forms of the microtubule-associated protein tau (encoded by the *MAPT* gene), often referred to as neurofibrillary tangles, also accumulate primarily in neurons, although they have been reported in other cell types of the brain [9, 10]. Beyond these “classical” neuropathologies, several additional cellular and molecular characteristics are associated with AD. For example, an increase in the number of reactive astrocytes and activated microglia (i.e. gliosis) has been described, especially in close proximity to plaques [11–13]. Interestingly, markers of gliosis seem to linearly increase across the course of disease despite a plateau in plaque pathology, suggesting independent mechanisms drive each cellular phenotype [14]. In his original report, Alois Alzheimer also described “adipose inclusions”, now recognized as likely lipid deposits, in glial cells of the brain [15]. Lipid accumulation in AD has been under-studied relative to other pathologies, but alterations in lipid metabolism and homeostasis are now emerging as a hallmark of AD brains [16–18]. A better understanding of these additional AD-associated features will likely shed light on mechanisms driving disease development across the lifespan.

While postmortem identification of these pathologies, particularly the presence of amyloid plaques and tau tangles, is still considered the gold standard for diagnosis, advances in brain imaging now allow clinicians to obtain accurate estimates of these features in living patients [19], which has aided in the clinical diagnosis of AD. Early detection is thought to be a critical aspect of effective therapeutic interventions, and there has been much work in the field aimed at identifying biomarkers that detect high-risk patients or those in early stages of disease [20]. Research has shown that measurements of Aβ and tau in cerebrospinal fluid (CSF) exhibit high diagnostic sensitivity, with low levels of CSF $A\beta_{42}$ and high levels of total tau or phosphorylated tau (particularly p-tau_{181}) capable of differentiating AD from mild cognitive impairment and other dementias such as frontotemporal dementia and Lewy body dementia [21–23].

AD is typically divided into two categories; early-onset AD (EOAD) where symptoms appear before the age of 65 years, and late-onset AD (LOAD), in which symptoms do not appear until after the age of 65 years. Despite the earlier age of onset and exacerbated clinical phenotypes in some EOAD patients [2], the two subsets share common pathological features and are both considered to be highly heritable. Estimates of heritability for EOAD are as high as 90–100% [24], while heritability estimates for LOAD are slightly lower, in the range of 60–80% [25]. Both forms of the disease can be further classified into sporadic or familial forms. Most sporadic cases present with late-onset symptoms, but instances of sporadic early-onset cases with no previous family history of disease have been documented [26]. Likewise, familial inheritance of AD is typically associated with early-onset forms of

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the disease, but large families with multiple individuals affected by LOAD are prevalent [27, 28]. While EOAD and LOAD have traditionally been considered distinct [29, 30], this review will consider the underlying genetic architecture of both forms of the disease, which in recent years has come to highlight a significant overlap between the subtypes. As no disease-modifying intervention currently exists, understanding the biological function of AD-associated variants (i.e the functional genetic architecture) across the spectrum of disease is likely to provide insight into potential therapeutic targets. Therefore, this review will also consider insights into the basic biology of disease provided by genetic studies, and discuss likely mechanisms involved in AD pathogenesis.

2. Genetics of AD

a. Monogenic causes of AD

The most well-studied forms of EOAD which have contributed most to our knowledge regarding disease etiology are those that are inherited in an autosomal dominant fashion, often referred to as autosomal dominant Alzheimer's disease (ADAD). ADAD is very rare, accounting for less than <1% of all cases of AD [2, 31–33], but the clear inheritance pattern facilitates the identification of causal mutations. A majority of ADAD families carry a pathogenic mutation in one of three genes: *APP*, presenilin 1 (*PSEN1*), or presenilin 2 (*PSEN2*) [2, 33]. To date, more than 50 highly penetrant mutations have been identified in *APP* [2]. These mutations are typically localized either near the sites where cleavage by secretases occurs or within the domain encoding the Aβ peptide. The overall effect of *APP* mutations is generally increased production and/or aggregation of amyloid, although the precise mechanism differs by mutation type and localization. For example, mutations occurring near the βsecretase cleavage site, such as the Swedish mutation (K670N/M671L), appear to result in increased production of total Aβ [34, 35]. Mutations in the Aβ domain itself alter the hydrophobicity and downstream aggregation propensity of Aβ peptides, leading to an increase in plaque load [36]. Other mutations such as those located near the C-terminal of the Aβ domain (e.g. V717L, V717I) influence the activity of g-secretase altering APP processing so that longer Aβ peptides more prone to aggregation are generated, including species 42–43 amino acids in length ($A\beta_{1–42}$ and $A\beta_{1–43}$) [37]. In contrast, a protective mutation in *APP* (A673T) identified in the Icelandic population [38] results in approximately a 40% reduction in the formation of amyloidogenic peptides. Together, this evidence has led to the development of the "amyloid cascade hypothesis" which posits that amyloid deposition is an initial causative event in a cascade of symptoms resulting in neurodegeneration and cognitive decline [39]. This hypothesis is further supported by the identification of additional *APP* genomic features associated with AD, including missense mutations inherited in an autosomal recessive fashion that drive amyloidogenic APP processing [40] and *APP* duplications which result in increased Aβ production [36].

The other EOAD-causative genes are highly homologous members of the presenilin gene family [41]. The first disease-causative mutations in these genes were identified in 1995 [42, 43], although it wasn't until 2000 that it was discovered these proteins are critical subunits of the γ-secretase complex responsible for processing of APP [44–46] and other membrane-bound proteins such as NOTCH [33]. Similar to some mutations in *APP*, familial EOAD

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mutations in *PSEN1* and *PSEN2* typically result in an increased production of longer and more aggregation-prone derivatives of APP such as $A\beta_{1-42}$ [47–49]. Mutations in *PSEN1* are the most common cause of ADAD; as of April 2020, over 350 mutations (some of unclear pathogenicity) have been identified (www.Alzforum.org). *PSEN1* mutations are estimated to contribute to around 80% of monogenic AD. *PSEN2* mutations are much rarer, with only around 30 mutations identified in ADAD families [2]. The effect of *PSEN2* mutations is more variable than either *PSEN1* or *APP* mutations, with age of onset in *PSEN2* mutation carriers ranging from 40 to 85 years of age [50, 51]. This suggests additional modifier variants may be capable of protecting against what are typically thought to be highly penetrant deleterious mutations. This raises the possibility that these "early-onset" mutations may play a significant and under-appreciated role in LOAD, an idea that will be explored later in this review.

b. *APOE* as a major genetic risk factor for AD

Beyond disease-causative mutations in *APP* and the presenilins, common polymorphisms in the gene *apolipoprotein E* (*APOE*) are the most significant genetic risk factor for AD [52–54]. *APOE* is a lipoprotein with various biological functions depending on the cell and tissue type in which it is expressed; high expression is observed in the liver, brain, and peripheral immune cells including monocytes and macrophages [55]. Broadly, *APOE* is responsible for maintaining lipid homeostasis by mediating lipid transport from one cell or tissue type to another [56]. In the central nervous system, *APOE* is primarily produced by astrocytes under normal conditions and transports cholesterol to neurons via *APOE* receptors, which are members of the low-density lipoprotein receptor (LDLR) family [57]. Under times of stress, *APOE* can also be produced by both neurons and microglia [47, 48].

Three different alleles of APOE exist, each encoding a unique isoform differentiated by the identity of the amino acids solely at positions 112 and 158, where either cysteine or arginine is present. These isoforms are referred to as APOEε2 (Cys112/Cys158), APOEε3 (Cys112, Arg158), and APOEε4 (Arg112, Arg158) [57]. Of the three alleles, *APOEε3* is the most common in all human populations, present in almost 80% of individuals [57]. *APOEε4* is less frequent (~14%) among the general population but drastically increases risk for AD in a dose-dependent manner [54, 57]; Caucasian individuals with two copies of *APOEε4* have on average a 15-fold increased risk for LOAD relative to those carrying no *APOEε4* alleles, whereas risk for individuals carrying only one *APOEε4* allele decreases to ~3 times that of non-carriers [58]. Interestingly, the effect of *APOEε4* has been reported to differ across ethnicities [58–61], suggesting additional variants may interact with *APOE* to mediate its effect on AD risk. For example, up to a 30-fold increase in disease risk was observed among Japanese individuals with two ε4 alleles as compared to a 15-fold increased risk in Caucasians [59, 60], whereas the association between ε4 and disease is reported to be weaker among African-American and Hispanic individuals [58, 61, 62] and nonexistent among Nigerian individuals [63]. Additionally, *APOEε4* has been shown to modify the age at onset in both EOAD and LOAD [64–66]. In contrast, APOEε2 appears to reduce risk for AD, with carriers of even one *APOEε2* allele in combination with *APOEε3* exhibiting only about half the risk of those carrying two *APOEε3* alleles [58]. However, *APOEε2*/*APOEε4* individuals are still at increased risk for AD, suggesting the APOEε4 isoform exhibits some

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dominant effect over the APOEε2 isoform [58]. Homozygous *APOEε2* individuals are relatively rare, making the dose-dependent effect of *APOEε2* difficult to assess in the general population. It has been suggested that *APOEε2* may protect against AD in a dose-dependent manner, with *ε2/ε2* individuals exhibiting up to a four-fold decreased risk [67, 68].

Despite the long-standing recognition of the impact of *APOEε4* on AD risk, the precise mechanism by which APOEε4 confers elevated risk for AD remains unclear [69]. Although the isoforms differ by only two amino acids, it has been demonstrated these alterations have profound impacts on the structure and function of the APOE protein [70]. For example, the ε2 allele has been demonstrated to exhibit impaired LDLR binding relative to both ε3 and ε4, and structural alterations unique to the ε4 allele shift binding preferences from small, phospholipid-rich high-density lipoproteins (HDL) to large, triglyceride-rich very-low-density lipoproteins (VLDL) in the periphery [70]. In the context of the central nervous system, APOEε4 has been linked to impaired Aβ clearance [71, 72], disruption of lysosomes and neuronal apoptosis [73, 74], as well as mitochondrial dysfunction [75]. Further investigations into these functions and how they may contribute to the development of disease will be critical in the coming years for targeted therapeutic development.

c. Genome-wide association studies (GWAS)

Despite the substantial increase in risk conferred by *APOEε4*, variation at this locus is estimated to explain only a portion of the heritability of LOAD [76], suggesting additional genetic variants play a significant role in determining an individual's risk for disease. Following the sequencing of the first human genome, platforms enabling the simultaneous genotyping of millions of single nucleotide polymorphisms (SNPs) across the genome were developed, providing a powerful framework with which to study the contribution of common genetic variation to complex diseases. This is most commonly performed through what is known as a genome-wide association study (GWAS), designed to test the association of genetic variants across the genome with a particular trait, often presence or absence of a disease. GWAS take advantage of the linkage disequilibrium (LD) structure across the human genome, where large blocks of the genome are inherited together [77]. Due to this phenomenon, a single genotyped SNP can tag an entire region of high LD, enabling the surrounding genomic sequence to be imputed, or predicted with high accuracy [78, 79] based on the reference human genome sequence. Genotype imputation allows data from different genotyping platforms to be harmonized and greatly enhances the feasibility of genome-wide studies without the need for expensive sequencing. However, if variants are rare (minor allele occurs in less than 1% of the general population [80]), they are unlikely to be captured by standard SNP genotyping or imputation using the publicly available reference resources [79]. The contribution of rare variants to disease must be assessed by other methods and will be discussed later in this review.

The first association studies covering most of the genome were published in 2007 [81, 82]. As these studies utilized a relatively small number of samples, only a single SNP in *APOE* reached genome-wide significance (typically considered $p < 5.0 \times 10^{-8}$, based on a Bonferroni correction for testing all independent SNPs in the human genome [83]). In fact,

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seven of the earliest GWAS, each of which used less than 2,000 cases, identified only *APOE* as significantly associated with AD [84–90]. This is likely due to small sample numbers, as GWAS requires a large sample size for sufficient statistical power to detect small-effect associations. This is because the tests require simultaneous testing of hundreds of thousands of SNPs across the genome, resulting in a high penalty for multiple testing corrections. The identification of *APOE* as the sole risk factor in small GWAS demonstrates that genetic variation at this locus is the most significant common genetic risk factor for LOAD, and genetic variation at other loci individually confer only small effects on disease risk.

In 2009, the first large-scale GWAS were published and loci outside of *APOE* were implicated in LOAD risk for the first time. The larger of these, involving over 16,000 individuals, identified SNPs on chromosomes 8 and 11 as significantly associated with disease risk [91]. The effects of these loci were attributed to nearby genes, clusterin (*CLU*) and phosphatidylinositol binding clathrin assembly protein (*PICALM*), respectively. However, due to the underlying LD structure, GWAS cannot identify which variant or gene in the identified region is truly causal. As multiple SNPs are inherited together in any given haplotype block, the GWAS SNP should only be thought of as 'tagging' an underlying association in its given genomic region. A second 2009 GWAS replicated the association of SNPs near *CLU* with LOAD and identified another locus on chromosome 1 as associated with disease, near the gene encoding the complement receptor 1 (*CR1*) [92]. These studies have since been expanded and many loci replicated across studies and sample sets [93–96], see Figure 1 and Table S1. The most recent meta-analysis of LOAD risk included data from over 95,000 individuals across 46 datasets and validated over 20 loci previously associated with disease, including well-replicated variants located near genes including *BIN1*, *CD2AP*, *CLU*, *ABCA7*, and *INPP5D*, among others [97] (Table S1). In addition, this GWAS identified novel variants not previously associated with the disease by standard GWAS, including variants near *IQCK* [97].

A majority of these initial GWAS have utilized data from populations of European ancestry due to sample availability and the ease of analyzing and interpreting data originating from a relatively homogenous population. However, the prevalence and incidence of AD is reported to vary widely by ethnic background, suggesting there may be ethnicity-specific contributors to disease risk [98]. To test this hypothesis, significant efforts have been made to expand AD GWAS to multiple diverse populations. As a result, several ethnicity-specific loci associated with disease have been identified, including variants on 18q23 in Caribbean Hispanics [99] and variants near *KCHN15* in Chinese [100]. Additionally, these studies have identified several loci that show conserved association with AD across population groups. For example, a large transethnic GWAS utilizing samples from Caucasians, African Americans, Japanese, and Israeli-Arabs identified several loci contributing to disease risk in all populations [101]. Consideration of multiple genetic backgrounds may also provide insight into the mechanisms by which common genetic variation influences disease risk. For example, *APOEε4* confers differing risk based on ethnicity, as discussed above. Studies comparing "global" ancestry (i.e. ancestry across the genome) to "local" ancestry (i.e. ancestral background of the *APOE* region alone) found that *APOEε4* risk was modified by local ancestry such that individuals that inherited the *APOEε4* allele (and surrounding region) from an African ancestor had a lower risk of developing AD than an individual who

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inherited *APOEε4* from a European ancestor [62, 102]. This finding suggests either 1) *APOE* genotype interacts with some surrounding genetic variants to dictate disease risk, or 2) protective alleles within the African *APOE* haplotype reduce the effect of *APOEε4* on disease, providing hypotheses to test in future studies.

Utilizing multiple ethnic groups in GWAS also enhances the ability of researchers to identify putative causal variants in associated loci due to variations in LD structure across populations [101]. As the number and identity of specific SNPs inherited together change, the preservation of association signals in the region allows researchers to infer which SNPs may be driving the signal versus those that are non-functional. While differences in LD structure and allele frequencies have traditionally presented a computational barrier to multi-ethnic GWAS, statistical models designed to account for these differences are constantly being developed and improved. Large-scale sequencing efforts targeting under-represented populations are also aiding in rare-variant detection and imputation, all of which will likely lead to improved consideration of ethnicity-specific genetic architecture in the context of AD risk [101]. Indeed, these approaches when applied to the *ABCA7* locus identified a deleterious frameshift deletion in *ABCA7* present in African Americans with AD at a higher frequency than either control African Americans or Caucasians [103]. While loss-of-function mutations in *ABCA7* have been identified as associated with disease risk in European populations [104–106], this study highlighted a novel pathogenic alteration that confers disease risk in an ethnicity-specific manner. Together, these approaches will help identify which therapeutic targets may be leveraged for the development of population-specific treatments or which may be useful across multiple genetic contexts.

d. Variations on traditional GWAS

In recent years, several variations on the traditional case-control and SNP-trait association studies discussed above have been developed. For example, researchers have hypothesized that the large effect of *APOE* genotype on AD risk may preclude the identification of smaller-effect variants. To test this hypothesis, researchers have re-analyzed data from the International Genomics of Alzheimer's Project (IGAP) following separation of *APOEε4+ and APOEε4−* subjects [107]. Among *APOEε4−* subjects, several novel associations between AD risk and SNPs near the *MAPT* locus were identified. Researchers then used genome-wide expression data to link these SNPs to expression of nearby genes *KANSL1*, *LRRC37A4P*, *C17orf69*, and *MAPT*. While these results suggest the identified SNPs may have multiple downstream targets, the identification of *MAPT* as a candidate target is particularly notable, as *MAPT* encodes for the tau protein which becomes aberrantly phosphorylated in AD. Specifically, SNPs protective against AD were associated with increased expression of *MAPT* exon 3, which has previously been associated with decreased aggregation of tau protein [108, 109] and protection from neurodegeneration [110]. As no disease-causative mutations in *MAPT* have previously been linked to AD, the findings here provide a putative mechanism by which regulation of *MAPT* splicing and exclusion of exon 3 may promote AD independently of *APOEε4* genotype. Additional analyses in stratified GWAS suggest association signals in the *MS4A* region were also stronger *in APOEε4−* subjects [107], while variants in the *PICALM* region exhibit stronger associations in

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APOEε4+ subjects [111], further suggesting independent mechanisms may partially contribute to AD across *APOE* genotypes.

Additionally, recent GWAS aimed at identifying genetic variants influencing risk for AD have moved beyond simple case-control designs, in part to reach the large sample sizes needed for sufficient power. In 2017, Liu et al. [112] proposed utilizing family history of AD as a proxy measurement for cases. In this design, individuals with a family history of AD are grouped as "cases" whereas individuals with no family history of disease are considered "controls". This enables the identification of patients who likely have a high genetic risk for AD but who may not yet present with clinical symptoms. Jansen et al. [113] expanded on this approach, differentially weighting various family history scenarios. For example, the "risk" of individuals with two parents affected with AD was upweighted relative to those with only one affected parent. In addition, the age of parents was taken into consideration. Cognitively normal parents who died at a relatively young age were not treated the same as cognitively normal parents who died at an elderly age, as the younger parents could have gone on to develop dementia later in life.

While proxy analyses themselves are less well-powered than traditional case control GWAS analyses, these approaches require less detailed phenotype data, thus enabling much larger sample sizes than standard case-control analyses (close to 500,000 participants in recent proxy GWAS compared to 94,000 in standard GWAS [97]), which require detailed clinical data for each participant. Proxy risk for AD, defined as a parental history of AD, exhibits strong genetic correlation with AD [113] and can thus be combined with existing GWAS datasets to enhance statistical power to find true genetic associations with disease. Together, these approaches show substantial genetic overlap with previous case-control GWAS and nominate a number of novel loci associated with proxy risk for AD [112–114]. While these results should be interpreted with some caution, as some proxy "cases" may never go on to develop dementia just as some individuals with no family history may go on to develop disease, the loci identified here provide further insight into the genetic architecture of AD and partially confirm family history of AD is a valid proxy measurement for AD risk.

In addition to alterations to study design and subject classification, several variations on the standard SNP-trait association test have been developed. One of the most common variations used in GWAS are gene-based association tests, which assign SNPs to nearby protein coding genes and aggregate the effect of all SNPs in any given gene on disease risk [115]. These approaches provide some advantages over SNP-based tests. First, as individual SNPs are aggregated together, there is a lower multiple testing penalty for gene-based tests. In addition, these tests are less reliant on LD structure present in a population and thus enable GWAS across genetically diverse populations. Several genome-wide significant loci not previously detected at the SNP level have been identified using gene-based approaches, including those assigned to *TP53INP* [115] and *PPARGC1A* [116]. At first glance, gene-based tests also seem to ease downstream interpretation as they implicate specific genes rather than individual SNPs in disease risk. However, the assignment of SNPs to genes can be relatively arbitrary and typically fails to consider the impact of SNPs on the function of genes which may not be the closest gene (e.g. SNPs within cell type-specific enhancers may be at some distance from the gene(s) they regulate).

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As mentioned above, a limitation of GWAS is that this approach cannot identify which variant or gene in the identified region is truly causal. Further work is needed beyond GWAS to understand the downstream biological impact of genetic variation in the region. Interpretation of GWAS hits is made more straightforward when GWAS SNPs themselves or nearby variants in high LD are located within coding regions of the genome, although this happens relatively infrequently [97, 113]. For example, only 2% of variants identified as associated with LOAD in the latest meta-analysis fell within exons [97]. Missense variants with predicted deleterious effects on protein function have been identified by GWAS in *TREM2*, *CR1*, *MS4A2*, *MS4A6A*, *TOMM40*, *IQCK*, and *CD33*, among others [97, 113], although many of these variants remain to be functionally validated using experimental systems. Many of these genes containing coding variants are highly expressed in microglia and function within the immune system, highlighting this pathway as critical for disease risk.

e. Polygenic risk scores

Despite the inherent complexities associated with GWAS, the information provided by these studies is valuable in order to better understand the genetic architecture of AD. Given the small effect sizes of loci other than *APOE* identified by GWAS, it is likely an individual's risk for AD is determined by the combinatorial effect of multiple variants acting together across the genome. Approaches to better understand how many associated variants may act together to predict risk of disease were first developed by the International Schizophrenia Consortium in 2009 [117]. These "polygenic risk scores" (PRS) have since been expanded upon in the context of AD and used for individualized risk prediction [118], which is important for the identification of at-risk individuals who may benefit from early therapeutic interventions, once developed.

Several diverse approaches can be taken when developing PRS from genetic data. One strategy is to simply identify an individual's genotype at each of the SNPs identified as associated with AD by GWAS and derive a weighted summary risk score based on the predicted effect of each SNP on disease risk. These scores can then be used to test whether the SNPs associated with disease in the initial GWAS population significantly predict disease in an independent sample. PRS incorporating only genome-wide significant SNPs have showed only a modest improvement in disease prediction over known risk factors such as *APOEε4*, age, and sex [119–121]. Another strategy designed to identify patients at risk for developing AD is the expansion of the PRS beyond SNPs reaching genome-wide significance in GWAS. This approach likely better captures the underlying genetic architecture of AD, since as discussed above GWAS SNPs simply act as tagging variants for a given risk locus and are often not themselves the causal variants. In addition, as mentioned, standard GWAS often suffer from being under-powered to identify true associations and as such, may miss variants modifying disease risk. By expanding PRS analyses to include variants below the genome-wide statistical cutoff, this approach allows for a more complete view of the genetic contribution to disease risk and seems to provide an improved method for risk prediction over more selective PRS or standard predictors such as *APOEε4* alleles, age, and sex [118, 122, 123]. However, evidence suggests the most accurate prediction results from a combined consideration of the PRS as well as these additional predictors

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(*APOE* genotype, age, and sex) [123]. In addition to overt disease risk, PRS scores derived from large numbers of common variants have been used to significantly predict age at onset of AD as well as likelihood of longitudinal progression from mild cognitive impairment to AD [118]. This supports the notion that AD is likely influenced by a large number of susceptibility genes, reflecting a complex set of biological pathways related to the disease [123]. In addition, the increased power provided by expansion of the PRS beyond GWAS risk variants suggests that there are still unidentified common variants that could contribute to disease.

One of the benefits of a PRS is that it can be used to compare the genetic architecture of the trait from which it was derived (in this case, LOAD), to the genetic architecture of other traits of interest. For example, Cruchaga et al. [26] compared a PRS generated using LOAD risk alleles identified by GWAS to disease risk in families with high LOAD prevalence (i.e. familial LOAD) as well as sporadic and familial EOAD. It was found that the burden (PRS) of LOAD GWAS variants significantly predicted disease risk and age at onset in both familial LOAD and sporadic EOAD [26]. Although GWAS variants were not associated with risk for familial EOAD inherited in an autosomal dominant fashion, the researchers noted that the sample size was small and that variant burden may have been associated with age at symptom onset in these families [26]. Together, these results suggest shared genetic architecture exists between both EOAD and LOAD, with some of the same loci influencing risk for disease in both cases. Overlap in the genetic architecture between AD and other diseases has also been reported, including type 2 diabetes [124] and immune-mediated diseases such as Crohn's disease [125, 126], although the precise mechanisms underlying this overlap remain to be elucidated.

f. Rare variants

Interestingly, estimates suggest common variants identified by GWAS explain only 30% of the heritability of AD [76], suggesting the genetic architecture of AD is more complex than that suggested by the "common disease, common variant" hypothesis GWAS is designed to test [127]. As mentioned above, the contribution of rare variants to AD cannot be adequately assessed by GWAS, although improved imputation methods are being developed to address this limitation [128]. The best way to assess the impact of rare variants on disease risk is by direct sequencing of either whole genomes or whole exomes. Fortunately, significant resources have been directed towards this effort in large populations of AD cases and controls through large initiatives such as the Alzheimer's Disease Sequencing Project (ADSP) [129]. Several additional cost-effective approaches have been developed, including targeted sequencing of selected loci, directed genotyping, and improved imputation of large cohorts [130].

One of the most well-studied rare variants that confers elevated risk for AD is the R47H variant in *TREM2* [131, 132]. Since its identification, the R47H variant has been associated not only with AD risk but also neuropathology, brain atrophy, and additional behavioral symptoms such as anxiety in AD patients [133–135]. Several studies have investigated the impact of the R47H variant on the function of *TREM2*, which is highly expressed on myeloid cells and known to be involved in the clearance of various cellular substrates

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including lipids, apoptotic cells, and Aβ plaques [136]. Evidence suggests the R47H variant reduces the ability of TREM2 to bind ligands such as lipidated APOE [137] and decreases the stability of the protein, potentially conferring reduced functionality [136]. Since the identification of R47H, additional rare variants in *TREM2* have been associated with AD risk [138–140], highlighting the critical role of this protein in the etiology of AD.

Several additional genes beyond *TREM2* have been identified as containing rare variants that modify risk for AD, including several others that are highly expressed by microglia in the brain [130] (Figure 1 and Table S1). For example, rare variants in *PLCG2* and *ABI3* have been associated with disease risk [130, 141]. *PLGC2*, which harbors a protective variant, encodes a transmembrane signaling enzyme implicated in lipid metabolism, calcium homeostasis, and immune response [130, 142]. *ABI3* has similarly been implicated in regulation of the immune response through interferon signaling [143] and also plays a role in actin cytoskeletal organization [144]. Additional genes identified to harbor rare variants associated with AD risk include *AKAP9*, *UNC5*, and *ADAM10*, although the strength of these associations and the role of these genes in disease etiology remains less well-established [145, 146]. Interestingly, several genes harboring rare variants, including *ADAM10* [114] and *SORL1* (discussed below), also emerge as candidates nominated by GWAS studies due to their proximity to AD-associated SNPs. This provides further evidence these genes are causally involved in disease etiology and facilitates the interpretation of complex GWAS loci.

One insight into the etiology of AD that has emerged due to rare variant sequencing is the importance of APP processing in both early- and late-onset forms of the disease. For example, rare variants in *SORL1* and *ABCA7* have been identified in family-based studies of LOAD [147–150], each of which have been associated with alterations in APP processing. *ABCA7*, an ATP-binding cassette transporter protein, is known to be involved in endocytosis and intracellular trafficking of APP [151]. Suppression of *ABCA7* led to increased β-secretase-mediated processing of APP and subsequent elevation of Aβ species [151]. *SORL1*, a sorting receptor located in neurons [152], astrocytes, and microglia [153] is known to direct APP toward non-amyloidogenic processing in the trans-Golgi network [148, 154]. Disease-associated mutations in *SORL1* have been linked with altered levels of APP at the cell surface and increased production of toxic Aβ species [147]. Notably, an enrichment for rare disruptive and putatively damaging variants in *SORL1* were also identified among EOAD cases [155, 156]. Common variants near *SORL1* have also been identified as associated with disease through GWAS [96], suggesting the same loci may contribute to both EOAD and LOAD.

In support, sequencing studies have identified rare variants in *APP*, *PSEN1*, and *PSEN2* that increase risk for LOAD [157]. Although causal variants in these genes are typically thought to be inherited in an autosomal dominant fashion, *de novo* variants in *APP*, *PSEN1*, and *PSEN2* have also been identified by sequencing in sporadic cases of EOAD that occur with no family history of disease [158, 159]. These data suggest *APP*, *PSEN1*, and *PSEN2* may play a larger role in the development of AD than previously thought and highlight the need to screen both EOAD and LOAD cases by sequencing to identify pathogenic mutations in these genes. Notably, most of the *APP* variants associated with disease have been evaluated

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in terms of their effects on Aβ production. However, Aβ-targeting strategies have largely failed to produce disease-modifying therapeutics, suggesting APP plays a role in disease pathogenesis beyond Aβ. Indeed, there is evidence that alternative APP-derived fragments as well as APP itself play important roles in the modulation of immune cell activation [160], protein clearance [161], and lipid homeostasis [162]. Together, this suggests the impact of these variants may have as-yet undescribed impacts on cellular function beyond Aβ generation, an idea which should be further explored in future studies.

Beyond the identification of risk factors of LOAD, rare variant sequencing studies have been beneficial in exploring the causal genes responsible for a subset of EOAD not explained by mutations in *APP*, *PSEN1*, or *PSEN2*. While mutations in these genes are the most well-studied mutations associated with EOAD, it is estimated that a significant portion of EOAD remains unexplained genetically [2]. Besides mutations in *SORL1* described above, mutations in *NOTCH3* were identified in a Turkish family with AD [163]. Targeted sequencing analyses have also provided insight into genetic modifiers of the age at first symptom onset in EOAD families [164, 165]. Given the overlap between EOAD and LOAD as discussed above, these modifiers may provide potential therapeutic targets for a more general population.

In summary, rare variant studies have yielded tremendous insight into mechanisms underlying the development of AD in diverse populations. Rare variants typically have a more deleterious impact on protein structure and/or function than common variants [166, 167] and thus have a larger effect on disease susceptibility than those identified by GWAS. This, combined with the effect that the gene impacted by the identified variant is often immediately apparent, makes it possible to more easily model the effect of the variant in cell-based assays or model organisms. While the variant itself may not contribute to disease across a broad population, the insight gained into disease mechanisms, particularly immune cell function and APP processing, by the study of genes identified by rare variant studies is likely to generate important therapeutic avenues in the coming years.

3. Functional genomic architecture

a. Understanding the regulatory function of non-coding risk variants

The goal of genetic studies of AD is to gain insight into the mechanisms underlying disease risk in order to develop targeted treatments to prevent or delay the onset of disease. However, translating the statistical associations identified by GWAS into biological insights remains a challenge. As mentioned above, GWAS variants often fall within regions of high LD such that multiple non-causal variants are inherited together with putative causal variant(s). A large portion of GWAS variants and even variants in high LD with the lead variant fall within non-coding regions of the genome, making their functional importance difficult to infer [168]. Much of the non-coding genome has regulatory functions, suggesting a majority of GWAS variants act by perturbing gene expression, presumably in a subset of disease-relevant cell or tissue types. However, regulatory elements can act on downstream target genes located a long distance away and have diverse effects depending on the context in which they are activated [169], making the specific genes impacted by GWAS SNPs difficult to identify. Further complicating the identification of downstream target genes is the

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fact that large numbers of protein-coding genes are often inherited together; for example in the most recent large GWAS of AD, implicated loci contained an average of 16 genes [97].

Due to these challenges, the earliest attempts to assign biological function to identified variants simply assigned SNPs by proximity to their nearest protein-coding gene. This approach has prioritized genes enriched for several major biological pathways including lipid metabolism, immune response, regulation of endocytosis, and protein ubiquitination, implicating these pathways in disease pathogenesis [170, 171]. Interestingly, there is evidence that groups of genes close together in chromosomal space function in similar biological pathways [172], suggesting this approach may be valid to identify overall pathways and functions perturbed by GWAS variants, although the specific genes investigated may not be direct targets of the causal variants in the region. For a number of genes including *APOE*, *ABCA7*, *BIN1*, *TREM2*, *SORL1*, *ADAM10*, and *SPI1*, there exists a number of functional studies and genetic evidence to suggest they are indeed the causal genes in their respective loci [97, 173], although their identification does not preclude the existence of additional pathogenic genes in these loci.

There has been a growing appreciation in recent years that simply assigning a GWAS-identified SNP to the nearest gene in linear genomic space may lead to false associations [174]. Instead, an increased emphasis has been placed on understanding the regulatory function of identified variants, as well as nearby variants in high LD (i.e. the functional genomic architecture). This has been greatly facilitated by the development of a variety of techniques designed to better understand how regulatory elements function to impact gene expression, which can happen in a variety of ways. For example, promoters proximal to the transcription start site of protein coding genes can recruit the binding of specific transcription factors, activators, or repressors [175]. Enhancers, short genomic sequences distally located from their target genes, confer additional cell- and tissue-type specificity to the regulation of gene expression. Enhancers are difficult to confidently identify from DNA sequence alone, but are instead defined by the presence of several functional marks including specific histone modifications that promote transcription [176] and by accessibility of local chromatin. Histone modifications can reliably be measured across the genome using chromatin immunoprecipitation followed by sequencing (ChIP-seq), while chromatin accessibility is typically measured by either DNase hypersensitivity analysis (DNase-seq) [168] or assay for transposase-accessible chromatin using sequencing (ATAC-seq) [177]. As enhancers are often located at a considerable distance from their target genes, it is believed they function by recruiting specific chromatin remodeling factors that promote the formation of chromatin loops, bringing the enhancer and promoter into close proximity [178]. A variety of assays now exist to capture this three-dimensional architecture, including various adaptations of chromosome conformation capture (3C) [179].

Regulatory elements across the genome exhibit a high degree of cell-type specificity, enabling the existence of diverse cell and tissue types as well as carefully orchestrated transcriptional responses to stimuli from a single genome. Identification of the precise cells and tissues in which regulatory elements containing AD risk variants are active would provide critical insight into where these variants may be acting to perturb gene expression and mediate functional effects that translate into modified risk for disease. This search has

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been facilitated by large-scale annotation projects such as the Roadmap Epigenomics Project [180], the Blueprint Project [181], and PsychENCODE [182]. These projects aim to generate, and make publicly available, high-quality reference annotation maps across a wide variety of human cell and tissue types. Combined with cell- and tissue-specific gene expression sets, these annotations can provide a comprehensive picture of how and where variants and associated regulatory elements may be impacting gene expression, and presumably, disease risk.

b. Cell-type specificity of AD risk

Several studies have assessed whether AD risk variants (both GWAS-tagged variants and associated variants in high LD) were enriched for localization to functional annotations from specific cell or tissue types [173, 183–185]. These studies largely expanded on the method described by Finucane et al. [186] for partitioning the genome into functional categories based on publicly available annotation data. This method combines annotations including “coding”, “intron”, “promoter”, and “enhancer” with cell-type specific annotations derived from measurements of four histone marks (H3K4me1, H3K4me3, H3K9ac, and H3K27ac) across over 200 different cell types. In combination with additional annotation information including chromatin accessibility as measured by DNase hypersensitivity, Gagliano et al. [183] identified a significant enrichment for AD-associated variants in functional annotations active in the “immune/hematopoietic cell” and “liver” categories, but not in other categories such as brain, cardiovascular, kidney, etc. These associations were observed whether *APOE* was included or not, confirming the enrichment was not driven by a single moderate-effect variant [183]. Similar enrichment for immune and liver cell categories was replicated by a second group utilizing an expanded set of tissue-specific annotations [185]. The identification of enrichment among “liver” datasets is particularly notable given that the liver is the principal site responsible for maintaining cholesterol homeostasis in the body [187]. Several factors implicate cholesterol metabolism in the pathogenesis of AD; a major role of *APOE* is to facilitate the transport of cholesterol from astrocytes to neurons in the CNS [188]. Interestingly, several genes expressed in the liver including liver X receptors (LXRs) have been suggested as potential therapeutic targets for AD [189–191]. Together, these findings suggest insights into the localization of genetic risk for AD identifies clinically relevant tissue- and cell-type enrichments.

Using a similar technique and annotation dataset, Huang et al. found a significant enrichment of AD SNPs in functional annotations attributed to hematopoietic cells, specifically monocytes and B-cells [173]. Using measurements of chromatin accessibility and histone modification maps, Tansey et al. [184] also sought to identify whether AD risk variants were preferentially located at DNase hypersensitivity sites across a panel of 38 tissues. Remarkably, immune cell types, specifically hematopoietic stem cells and primary blood monocytes, were again identified as primary cell types containing areas of accessible chromatin in which AD-associated variants were preferentially located [184]. No enrichment was observed for AD variants in brain-specific DNase sites, although the only two datasets included were generated from fetal tissue, which is likely not reflective of the regulatory chromatin landscape observed in adult or diseased brains. A targeted secondary analysis revealed an enrichment for AD variants in regions of open chromatin as measured by ATAC-

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seq in microglia [184], suggesting a lack of signal in brain tissue is due to the heterogeneity of the bulk tissue from which it was derived. This is supported by a recent identification of the enrichment of AD-associated variants in enhancers active in primary human microglia [192]. Together, these studies suggest the genetic architecture of AD primarily impacts regulatory elements active in cells of the immune system.

Given the critical role of regulatory elements in regulating gene expression, it can be hypothesized based on the above findings that AD variants likely modify risk for AD by having a functional impact on gene expression in immune cells, particularly myeloid cells such as monocytes, macrophages, and microglia. This idea is supported by studies showing that alleles associated with AD show an effect on gene expression specifically in monocytes. Raj et al. [193] performed genome-wide transcriptional profiling of T cells and monocytes, representative cells of the adaptive and innate immune system, respectively. Genetic mapping was then performed in order to identify genomic regions responsible for regulating quantitative gene expression levels, also known as expression quantitative trait loci (eQTLs). AD-associated variants were enriched for colocalization with eQTLs specifically regulating gene expression in monocytes, but not in T-cells, demonstrating AD variants have a cell-type specific effect on gene expression. Huang et al. [173] leveraged this information to identify *SPI1* as the most likely candidate causal gene in the genomic region traditionally annotated as the *CELF1* locus due to the proximity of the lead GWAS SNP to the gene *CELF1*. Instead, it was shown that variants in high LD with the lead SNP were significantly associated with regulation of SPI1 levels in myeloid cells, likely causally modifying disease through this mechanism [173].

Exactly how AD-associated variants influence myeloid cell gene expression is still being explored. One plausible mechanism is that these variants disrupt the binding of lineage-specific transcription factors and alter the transcriptional landscape of these cells. In support of this hypothesis, regions of open chromatin in human monocytes, macrophages, and microglia [173, 184] containing AD risk variants were shown to be enriched for binding motifs of the transcription factor *SPI1*, providing a mechanistic explanation by which alterations in *SPI1* levels conferred by variants in the *SPI1* locus may have widespread effects on cellular function. *SPI1* is particularly important for myeloid cell differentiation and function, and has been linked to the ability of microglia to clear pathogens and cellular debris [173, 194]. AD-associated variants may also alter sites typically targeted for reversible epigenetic modifications that regulate gene expression such as methylation or acetylation. Early clues to the involvement of epigenetic modifications in AD came from observations that altered methylation at the promoters of *APP*, *PSEN1*, and *APOE* could modify risk for disease. Targeted studies have revealed methylation alterations at additional loci associated with disease [195–197], and two independent genome-wide studies recently identified a differentially methylated region in the *ANK1* gene as associated with the burden of AD pathology [198, 199]. Additional possible explanations include altered recruitment and/or binding of chromatin remodeling factors such as CTCF or alterations in promoter-enhancer interactions. It is likely that AD risk variants will have diverse effects on gene expression and will need to be investigated individually to gain a complete understanding of how variants function to modify AD risk.

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While no enrichment of AD-associated variants were identified in bulk brain datasets, the brain is still the organ most affected in AD, and the regulation of gene expression in this critical tissue is undoubtedly important for disease pathogenesis. Several studies have performed targeted analysis of the impact of identified AD SNPs on brain-specific gene expression [200–202]. While the use of bulk datasets does not provide specific information about the cell types through which AD variants act, they still provide useful information as to which genes may be targeted by GWAS SNPs. Advances in single-cell techniques will enable the further interrogation of these identified eQTLs and enhanced understanding of which cell types are critical to disease etiology. Based on data from peripheral cells and select microglia-specific datasets [184, 192], it is likely the regulation of gene expression in microglia will emerge as critical to disease pathogenesis. Identification of specific target genes and their downstream impact on cellular function will be particularly important, as it is still relatively unclear as to how these cells are involved in promoting or protecting against disease. While microglia exhibit several beneficial functions in the brain such as clearance of cellular debris and orchestration of appropriate immune responses, their chronic activation can lead to toxic neuroinflammation and aberrant pruning of synapses [203, 204]. Insight into how risk or protective variants alter these critical cellular functions should provide insight into how to harness the beneficial properties of these cells for therapeutic development. It should be noted that most of the currently available functional annotation data is derived from healthy donors. Given the dynamic changes in gene expression observed in disease, it may be necessary to investigate the regulatory landscape of cells under a variety of conditions in order to gain a full picture of how the localization of AD risk variants changes with time, cellular stress, and under disease conditions.

4. Genetic architecture of AD endophenotypes

The GWAS discussed above were primarily performed on case/control datasets and provide information regarding the genetic architecture of disease risk. However, this approach does not provide information about other aspects of the disease such as age of onset or disease progression, or as discussed, biological mechanisms involved in disease pathogenesis. In addition, the case/control design can be complicated by pre-symptomatic AD patients who are misclassified as “controls” due to a current absence of clinical symptoms and non-AD dementias misclassified as probable AD. To both better classify cases and controls as well as gain insights into additional mechanisms underlying disease, many groups have turned to the use of *endophenotypes*. Endophenotype, a term coined in 1966, is defined as a feature of disease that can be objectively and quantitatively measured across individuals, and that which exists between the behavioral symptoms of a disease (e.g. cognitive decline in AD) and its underlying (e.g. genetic) cause [205]. When an endophenotype reliably distinguishes between cases and controls, it can be used as a biomarker enabling the identification of at-risk populations and enhancing diagnostic sensitivity. For example, “core” biomarkers and endophenotypes of AD include low CSF levels of $A\beta_{1–42}$, shown to indicate reduced clearance of $A\beta_{1–42}$ from the brain, and elevated CSF tau (both total tau and phosphorylated tau), thought to indicate neuronal degeneration or injury [206].

Using quantitative endophenotypes as the primary endpoint for GWAS instead of a binary classification of presence/absence of disease enables a more precise phenotype

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measurement, thus increasing the power for identification of genetic variants associated with disease [207] (Figure 1 and Table S1). In addition, this approach greatly facilitates interpretation of the downstream functional consequences of the prioritized loci. In targeted analyses, it has been shown that genetic variants that increase risk for AD also influence CSF $A\beta_{1-42}$ levels, including pathogenic mutations in *APP*, *PSEN1*, and *PSEN2*, as well as *APOE [208–210]*. These results have been expanded upon with large GWAS using CSF $A\beta_{1-42}$ and/or tau levels as the trait of interest. These analyses have identified variants in the *TREM2* cluster as associated with these quantitative endophenotypes, as well as variants in the *ABCA7* and *FERMT2* gene regions [23, 211]. The identification of distinct loci for $A\beta_{1-42}$ versus tau traits suggest these endophenotypes are regulated, in part, by distinct genetic mechanisms. While the majority of loci overlap with GWAS loci, several novel loci not previously associated with AD risk have also been identified through these analyses, including variants located near the genes *GLIS3, GLIS1, GEMC1*, and within *SERPINB1* [23, 211]. Notably, several of these novel variants, including those near *GLIS1* and within *SERPINB1*, were associated with additional aspects of disease including risk, age at onset, and progression [211], suggesting improved phenotype definition afforded by quantitative measurements is capable of identifying small-effect loci that may be missed by a case/control GWAS.

While $A\beta_{1-42}$ and tau are considered “core” endophenotypes or biomarkers of AD, additional quantitative measurements have been observed to be related to AD risk. For example, the levels of soluble TREM2 (sTREM2) have been shown to increase five years before symptom onset in autosomal dominant forms of AD [212]. sTREM2 is thought to be produced in one of two ways; either by cleavage of TREM2 by proteases such as ADAM10, ADAM17, and γ-secretase, or by alternative splicing which generates a short isoform lacking a transmembrane domain (~25% of *TREM2* transcripts) [134]. sTREM2 is then released into the CSF where it can be measured, and has been shown to correlate with CSF levels of tau [213, 214], suggesting it may be a relevant secondary biomarker of disease progression. Common variants in the *MS4A* gene cluster were shown to significantly regulate sTREM2 levels in CSF [134], demonstrating regulation of this endophenotype is orchestrated by genetic variants that also modify risk for disease. CSF levels of APOE protein have also been suggested to act as a valuable endophenotype for AD [215], along with levels of various additional proteins, the clinical and biological relevance of which remain to be elucidated [216–218].

While the studies discussed above have largely utilized CSF biomarkers, considered advantageous due to the proximity of this compartment with the brain, collection of CSF samples is quite invasive. Recent advances in imaging technology have enabled high-resolution scanning of the brain in living patients, facilitating non-invasive identification of a number of imaging-based endophenotypes for AD. For example, amyloid burden across the brain can be localized and quantified through the combined use of a radiolabeled ligand such as Pittsburgh B and positron emission tomography (PET) imaging [219]. PET imaging can also be used to measure glucose metabolism in the brain through the utilization of a radiolabeled alternate form of glucose, 18F-fluorodeoxyglucose (FDG) [220]. AD patients exhibit decreased uptake of FDG on PET [220], and this measurement can be used to differentiate AD patients from other clinical diagnoses [221], suggesting FDG-PET provides

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an additional reliable endophenotype of AD. The final major class of imaging endophenotypes are thought to be indicative of neurodegeneration and include traits such as increased ventricular volume and reduced hippocampal volume. These structure-based endophenotypes are particularly valuable, as they reliably predict cognitive decline [222], are heritable [223, 224], and are readily quantifiable by magnetic resonance imaging (MRI).

Programs such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) have facilitated efforts to perform standardized imaging across cohorts of AD cases, those diagnosed with MCI, and cognitively normal controls [225]. These efforts have greatly expanded the number of imaging datasets available and have enabled investigation of the genetic architecture of imaging-related AD endophenotypes. However, imaging remains a relatively expensive technique and as such, the sample sizes of well-characterized cohorts are much smaller than those utilized for traditional case-control analyses. The first investigations into the genetic architecture of imaging endophenotypes largely utilized a candidate gene approach, where genes previously implicated in AD risk were tested for association with imaging traits. SNPs in and around candidate genes including *APOE*, *BIN1*, *SORL1*, and *CR1* have been associated with traits including medial temporal lobe atrophy and cortical thickness [225–228], suggesting these AD risk variants may act, in part, by regulating neurodegeneration. Despite relatively small sample sizes, GWAS on specific quantitative imaging phenotypes have been conducted by several groups. Interestingly, while several genes previously implicated in AD (including *APOE* and *PICALM* [229]) have been associated with imaging endophenotypes, a large number of novel loci and genes have been nominated by these analyses [222, 229–231] (Figure 1 and Table S1). As the quantitative nature of endophenotypes results in improved phenotype definition beyond traditional case-control analyses, the loci identified by imaging studies may contain novel genes contributing to the etiology of AD that may have been missed by traditional approaches. Groups are actively working to integrate multiple imaging traits together, providing an even further improved diagnostic classification [232, 233] which will likely advance our understanding of brain-wide pathologies that occur in AD.

In order to more accurately model the overlap between the genetic architecture of AD risk and regulation of endophenotypes, several groups have turned to using PRS to evaluate overlap between traits. For example, Deming et al. [211] compared a PRS derived from genome-wide significant SNPs associated with AD to levels of CSF pathologies measured in an independent patient cohort. Although in their analysis the individual GWAS SNPs were not significantly associated with CSF levels of $A\beta_{1–42}$ or tau, together the additive risk conferred by all variants was significantly associated with both $A\beta_{1–42}$ and tau. Similarly, it has been demonstrated that increased genetic risk for LOAD as defined by a high PRS is associated with several imaging endophenotypes, including decreased cortical thickness in brain regions known to be vulnerable to degeneration in AD, decreased total brain volume, and decreased hippocampal volume [234]. Across studies, the association of GWAS-derived PRS with endophenotypes remained significant even after removal of *APOE*, suggesting the contribution of small-effect GWAS loci to AD risk is, in part, mediated by the effect of these variants on specific neuropathologies, including $A\beta_{1–42}$ and tau levels as well as neurodegeneration.

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Together, these endophenotype-focused GWAS analyses highlight the overlap in genetic architecture across various aspects of AD and provide important insight into the mechanisms by which variants modifying disease risk may act. The enhanced patient classification scheme afforded by quantitative biomarkers will likely facilitate enhanced power to diagnose AD in general, possibly providing a framework in which to identify subtypes of patients with distinct endophenotype profiles. It has been hypothesized that several subtypes of AD exist [235], and improved identification and diagnosis will likely enable targeted intervention and therapeutic development. As the collection of CSF samples remains invasive and imaging is quite expensive, both approaches are relatively difficult to utilize across very large samples such as those required for well-powered GWAS. As such, there has been an emphasis in recent years to identify blood- or plasma-based biomarkers for disease, the search for which is still ongoing [217]. These approaches will likely provide valuable alternatives to CSF and imaging and yield important insight into how identified risk variants might influence disease onset, severity, and progression.

5. Genetic architecture of AD: beyond SNPs

a. Somatic variation

Typically, an organism is considered to have one DNA sequence across all cells in the body. However, recent advances in single-cell genomic technology have identified a surprising amount of genetic mosaicism, that is, accumulation of non-inherited SNPs, indels, and copy number variants not present in germline cells. Perhaps the most striking example of this in AD is the finding of a sporadic AD patient who harbored a disease-causative mutation in *PSEN1* only in approximately 14% of brain cells [236]. The patient was originally classified as negative for *PSEN1* mutations after peripheral blood was drawn and blood DNA sequenced, but after DNA was obtained from the cerebral cortex, evidence of a cell-type specific mutation was observed. One offspring of the affected patient inherited the *PSEN1* mutation in all cells of her body and exhibited signs of dementia by age 27, indicating the degree to which mutations that are expressed throughout the body have a profound effect on disease severity [236]. Additional somatic mutations in genes known to confer risk for AD such as *APP* and *SORL1* [237] have been identified in the brains of both EOAD and LOAD patients [238, 239]. In general, neurons from AD patients have been observed to have an enriched number of somatic variations not observed in peripheral DNA [239, 240].

Several mechanisms may contribute to the abundance of somatic mutations in the AD brain. Transposable elements (TEs), mobile genetic sequences present in all eukaryotic genomes, account for up to 45% of the human genome. When TEs, especially retrotransposons, are activated, they mobilize through an RNA intermediate and can cause somatic mutations or large genomic rearrangements via their insertion into random segments of the genome [241, 242]. Under normal conditions, surveillance mechanisms including those associated with DNA repair and chromatin remodeling function to repress TE activity and largely maintain genomic stability [243]. However, with aging, the efficacy of these systems is known to be reduced, providing a genomic environment in which TEs may become activated and contribute to somatic mutagenesis [244, 245]. Neuropathologies such as tau have been observed to promote activation of TEs, providing an additional stimulus which may drive TE

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activation in the AD brain [245]. In addition, aberrant re-entry of neurons into the cell cycle has been hypothesized to be a mechanism underlying development of AD. As these cells do not typically divide, DNA replication stress and insufficient repair mechanisms may contribute to the development of somatic mutations in neurons [246], rendering these cells uniquely susceptible to eventual death as is observed during the neurodegenerative phase of AD. Together, this work suggests the genetic architecture of AD may not be completely accurately represented by studies utilizing peripheral blood DNA, which should be considered when interpreting the results of GWAS and other rare-variant sequencing studies.

b. Copy number variation

GWAS are uniquely designed to identify the impact of common polymorphisms on complex traits. However, SNPs are not the only mechanism by which genetic variation contributes to external traits. Another main source of genetic variation are copy number variants (CNVs) in which regions of the genome have been duplicated, inserted, or deleted [247]. CNVs may alter gene dosage and have a profound impact on both gene and protein function. In addition, CNVs may span multiple genes and have a measurable impact on more than one target [247]. It is estimated about 15% of the human genome is affected by CNVs, suggesting these may have a substantial impact on disease susceptibility. Gene duplications of *APP* are well-known to cause AD, with as many as 25 duplications of variable length associated with AD in EOAD families [2]. Neuropathological examination of patient brains harboring *APP* duplications show abundant plaque and tangle pathology as well cerebral amyloid angiopathy (CAA), which is characterized by deposition of Aβ in the cerebrovasculature and by hemorrhagic stroke [248, 249]. In addition, *APP* gene duplications that result from trisomy of chromosome 21 (Down's Syndrome) result in near-complete penetrance of AD neuropathology and increased incidence of dementia by age 30–40y [250, 251]. Rare autosomal CNVs in genes besides *APP* have been implicated in EOAD [252], demonstrating consideration of genetic variation beyond SNPs can improve our understanding of the genetic architecture of AD. CNVs have also been identified as modifying risk for LOAD; a functional CNV in the gene *CR1* modifying isoform production was shown to increase risk for LOAD in two populations [253], among others [254–256].

6. Additional Considerations

a. Sex-specific genetic architecture

AD is well-known to be more prevalent among elderly females, although it has been difficult to elucidate whether this is simply attributable to the longer lifespan of women [1, 257]. Notable sex differences in the clinical and pathological presentation between the sexes exist, each of which have been extensively reviewed previously [258–261]. For example, studies have reported more rapid cognitive decline in women, increased susceptibility to neuropathology such that each unit increase of AD pathology confers a 22-fold increase in risk for AD in women compared to a 3-fold increase in males, as well as important differences in clinical and pathological disease presentation [262]. One putative explanation for these differences is the presence of sex-specific genetic factors that influence risk for AD, although these have been difficult to identify in a systematic way. Several studies have demonstrated *APOE* genotype has an exacerbated effect on disease risk in females [58].

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Notably, *APOE* has been associated with sex-specific alterations in CSF tau levels and disease progression but not robustly with CSF $A\beta_{1-42}$, suggesting sex-specific effects of *APOE* genotype emerge downstream of amyloidosis [258]. Given the large sample sizes needed for sufficiently powered GWAS, investigation of sex-specific effects of loci outside of *APOE* on AD risk are less well-explored. A recent sex-stratified GWAS identified a male-specific protective variant located on chromosome 7 that conferred specific protection from tau pathology and was associated with delayed age at onset [263]. Several additional loci, including *APOE* [264], have been identified as exhibiting sex-specific association with AD endophenotypes, providing insight into biological mechanisms by which females may be at increased risk for AD [258, 265]. Overall, there is a critical need for a more detailed exploration of the mechanisms by which males and females exhibit differential susceptibility to AD, although current evidence points to important differences in the AD genetic architecture across sexes.

b. Missing heritability of AD

Despite decades of research, our understanding of the genetic architecture of AD is far from complete. Current estimates suggest only about 30–40% of the heritability of AD is explained by identified GWAS variants, leaving over 25% of the variance unexplained by known genetic factors [76]. Some of this “missing heritability” can be attributed to low frequency variants not evaluated in the general population or to variations in the epigenetic profile of patients not captured by standard genetic evaluation, both of which were discussed above. In addition, most GWAS are conducted using a standard additive model [266], where it is hypothesized heterozygous variant carriers exhibit a phenotype approximately intermediate in severity relative to each homozygous genotype. However, it has been estimated that up to 90% of EOAD may be caused by recessive mutations [24]. As such, it can be hypothesized that at least some percentage of LOAD is also caused by recessive mutations, where heterozygous mutation carriers will appear phenotypically similar to homozygotes carrying two copies of the dominant allele. These recessive effects may be missed by standard GWAS. Analyses aimed at genes which influence disease in a non-additive fashion have identified novel candidate genes for obesity and type 2 diabetes [267], suggesting these approaches may be useful in identifying recessive mutations that modify an individual’s risk for AD.

The large variability in the age at onset of AD symptoms even among families who share common pathogenic mutations [31] suggest variants in an individual’s genetic background modify the effect of specific variants on phenotypic penetrance. This highlights the possibility that extensive gene-gene interactions may contribute significantly to the genetic architecture of AD such that the effect of any AD-associated variant may largely depend on surrounding genetic context [268]. Hohman et al. [268] performed the most extensive analysis of gene-gene interactions in AD to date and identified three gene-gene combinations which significantly interact to determine an individual’s risk for AD, suggesting gene-gene interactions do indeed contribute to the heritability of AD. Similarly, an individual’s genetic background has been reported to influence how they respond to environmental exposures or lifestyle factors [269]. Several modifiable risk factors have been associated with AD risk across populations, including educational attainment, obesity,

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cholesterol levels, social isolation, alcohol consumption, and exposure to pesticides [269, 270]. It has been shown that an individual's genetics affects the impact of many of these risk factors on AD; for example, *APOEε4* carriers with low self-reported exercise levels exhibited an increased risk for disease beyond those with either *APOEε4* or low exercise alone [271]. However, genome-wide gene-environment interactions are difficult to identify for various reasons, including the fact that data regarding an individual's environmental exposures and/or lifestyle choices are unreliable due to incomplete recall or reporting, inconsistent dose, timing, and duration of exposure, and/or additional confounds produced by unreported exposures [272]. More thorough prospective analyses that document an individual's lifestyle choices and environmental exposures prior to disease onset (such the NIH's All of Us program) will provide enhanced resources through which to examine the environmental impact on disease risk. Combined with statistical approaches such as Mendelian Randomization [273, 274] that provide estimates of the causal association between environmental exposures (or other lifestyle factors) and disease risk, these approaches will likely enable an improved understanding of how genetics and environment interact to predict disease risk.

Finally, some of the "missing heritability" of AD may be attributable to the heterogeneity of the disease itself. Across the population, patients clinically diagnosed with AD display a wide variation in the onset, duration, and severity of symptoms across multiple functional domains and may experience deficits in cognitive function, speech, mood regulation and psychosis, motor function, and regulation of circadian rhythms [275]. This heterogeneity is observed even in carriers of highly penetrant *APP* and *PSEN* mutations [276], suggesting additional factors such as background genetic modifiers or even non-genetic lifestyle factors play a substantial role in dictating disease risk and severity. In addition, although AD is defined pathologically by the presence of Aβ and tau tangles, these pathologies often do not occur in isolation. A significant majority of patients diagnosed with AD also exhibit signs of additional pathologies including vascular lesions, Lewy bodies, TDP43 pathology or cerebral amyloid angiopathy [275]. First, this suggests patients diagnosed with clinical AD and included in many GWAS as "cases" may in fact not be pure AD cases but rather be suffering from a type of dementia due to mixed causes. As distinct genetic variants likely contribute to each aspect of any individual case, including these complex cases in the AD pool will likely reduce statistical power to identify genetic variants associated specifically with AD. Even among patients with neuropathologically confirmed AD, the clinical and pathological heterogeneity of the disease itself has led to the hypothesis that specific genetic variants may be associated only with specific aspects or features of the disease. This has led many to attempt to identify distinct subtypes of AD [235, 277]. In theory, the utilization of distinct subtype classification schema would provide a cleaner trait to test for genome-wide genetic association. Although this has proven difficult in practice, this should be an area of focus in coming years, as subtype-specific analyses may ultimately provide useful information for the development of personalized therapeutics for individual AD patients depending on their symptom spectrum.

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c. Use of model systems that reflect the genetic architecture of disease

The substantial increase in our understanding regarding the genetic architecture of AD has resulted in the development of novel model systems in which to experimentally investigate mechanisms driving disease. Since the discovery that genetic variants are enriched within regulatory regions active in myeloid cells [173, 183, 184], a large emphasis in the field has been placed on improving resources to better model the impact of these variants in a disease-relevant context. This has resulted in highly efficient techniques to derive microglia-like cells from human induced pluripotent stem cells (iPSCs) [278, 279]. As these cells are typically difficult to access from human patients, this represents an exciting development in experimental capabilities. The addition of microglia-like cells engineered by genome editing to express disease-relevant mutations to established protocols for neuron/astrocyte co-culture [280] and the development of brain organoids is likely to greatly contribute to our understanding of how these cells contribute to disease [281]. Together, these approaches provide a tractable human model system in which to study AD [282].

As microglia are intrinsically designed to respond to their environment, it is likely disease-relevant insights into the impact of disease-associated variants on their biological function can best be elucidated via *in vivo* experiments. To this end, innovative transplantation methods have been established to implant hematopoietic stem cells (microglia precursors) or microglia themselves directly into the brains of mouse models, where they have been shown to fully integrate and differentiate into mature microglia [278, 279, 283]. Due to the strong biochemical, developmental, physiological, and genetic similarities between the mouse and human, the mouse represents an incredible resource for neuroscience research and has been used for decades to gain insight into mechanisms underlying the development of AD *in vivo [284, 285]*. However, traditional models created by incorporating a highly penetrant mutation in *APP*, *PSEN1*, or *PSEN2* onto a single inbred background strain have largely failed to yield successful results in human clinical trials [286, 287]. Recent attempts to create improved mouse models have benefitted from the insights regarding the genetic architecture of AD described here. Widespread efforts to develop new models based on specific AD-associated variants have begun (e.g., www.model-ad.org), which promise to yield insight into the impact of these variants on gene expression and cellular function. In addition, efforts to expand existing AD mouse models through the inclusion of genetic diversity [288, 289] have resulted in resources that show a more significant overlap with human AD transcriptional profiles than models on a single genetic background [288], suggesting these genetically diverse models may represent improved preclinical resources than traditional approaches. In support, a PRS derived from human LOAD GWAS [96] showed significant association with cognitive outcomes across genetically diverse AD mice at 14 months of age [288], suggesting similar genetic mechanisms underlie AD susceptibility across species. This has important implications for the general use of AD mouse models and demonstrates the importance of considering genetic diversity in preclinical studies.

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7. Conclusions and future directions

In summary, substantial advances in genetic and genomic technologies over the last thirty years have significantly contributed to our understanding of the genetic architecture of AD (Figure 1). Several genes including *APP*, *PSEN1*, *PSEN2*, and *APOE* have been shown to exhibit relatively large effects on disease susceptibility, with the remaining implicated loci having a much smaller individual impact on AD risk. It is only in recent decades that the technologies to 1) identify, and 2) effectively link these genetic variants to their downstream biological impact have become available. Specifically, advances in broad -omics technologies now enable genome-wide sampling across thousands of individuals with differing genetic backgrounds, providing unprecedented insight into how genetic variation leads to changes not only in RNA and protein expression, but also epigenetic signatures, chromatin accessibility, and long-range 3D genomic interactions. Integrative approaches are emerging as highly effective for identifying the specific target genes through which AD risk variants act. Indeed, we now understand that common genetic variants impacting AD are not randomly distributed across the genome. Instead, these variants seem to be enriched for localization to regulatory elements active largely in human monocytes, macrophages, and microglia.

In addition, advances in genome editing technologies and model organism development will greatly facilitate the understanding of the functional genetic architecture of AD. As there is currently no cure for AD, together these advances represent a significant and exciting opportunity to explore the therapeutic utility of identified candidate genes and pathways. A better understanding of the genetic architecture of a complex disease such as AD is likely to provide several important benefits to patients and their families as well as clinicians and researchers. First, identifying and understanding the biological function of AD-associated variants (i.e the functional genetic architecture) is likely to provide insight into potential therapeutic targets. Second, genetic variants associated with disease can be used to identify at-risk populations that may benefit most from early interventions or specific therapies. When combined with imaging and/or CSF biomarkers, genetic variants may provide an important tool by which to better understand a given patient's risk or disease status. Indeed, nearly all clinical trials include stratification by *APOEε4*, an acknowledgement of the importance of this risk factor. As an alternative to focusing on one or even a few genetic variants, a better understanding of the genetic architecture of AD will also enhance our ability to calculate PRS that broadly encompass genetic risk. At the present time PRS only provide a modest advantage over APOE genotype alone, but improved PRS in combination with profiling of non-genetic risk factors such as various lifestyle factors may further improve our ability to stratify patients based on risk. With this information, we may be able to provide individualized recommendations, including both pharmacological and non-pharmacological approaches (e.g. improved diet and exercise), to those most at risk. Finally, additional characterization of how the architecture of disease differs across ethnicities, sexes, and disease subtypes will provide important insight into the specific populations in which each identified therapeutic may be most effective, a consideration which will likely prove critical in the coming years.

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Supplementary Material

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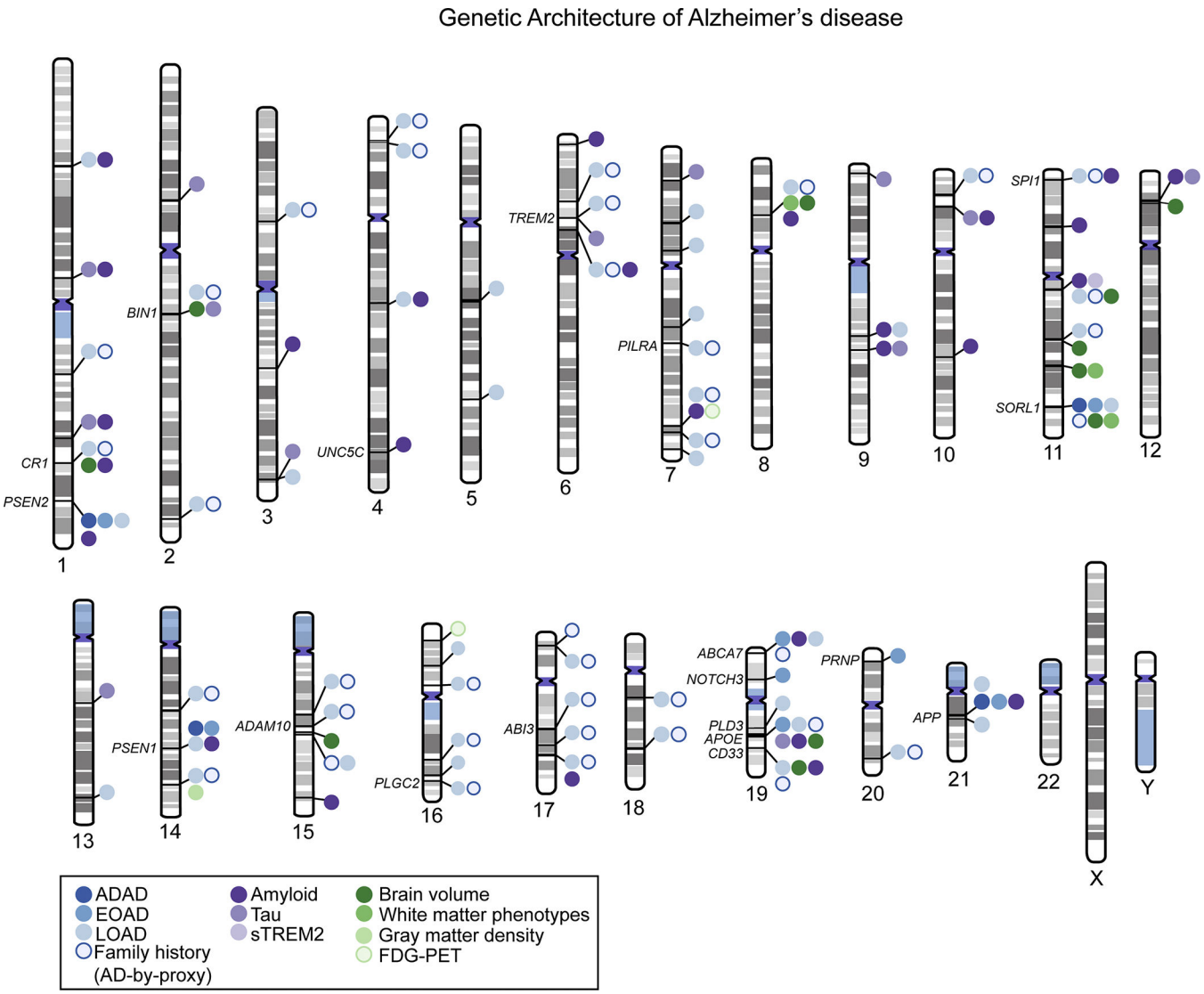

Figure 1: Genetic loci associated with Alzheimer's disease (AD).

A literature search was used to identify studies reporting genomic loci associated with either risk for AD or various endophenotypes including cerebrospinal fluid measurements of amyloid and/or tau, amyloid deposition as measured by positon emission tomography (PET) or postmortem studies, and brain glucose metabolism as measured by fluorodeoxyglucose (FDG)-PET. Genes with sufficient functional evidence to suggest they are the causal gene in their respective loci are annotated on the figure. Unlabeled loci indicate the causal gene in the region is still unknown. Source information for this figure can be found in Supplementary Table 1. Phenogram was constructed at http://visualization.ritchielab.org/phenograms and modified in Adobe Illustrator for clarity.