The Spectrum of Genetic Risk in Alzheimer Disease

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Abstract

Alzheimer disease (AD), the most common dementing syndrome in the United States, is currently established by the presence of amyloid-β and tau protein biomarkers in the setting of clinical cognitive impairment. These straightforward diagnostic parameters belie an immense complexity of genetic architecture underlying risk and presentation in AD. In this review, we provide a focused overview of the current state of AD genetics. We discuss the discovery of familial autosomal dominant genes, the identification of candidate genes associated with AD, and genetic variants conferring higher risk of developing AD compared with the general population. In particular, we discuss important features of AD risk due to the *APOE* ε4 allele. In addition to risk, we describe how the field has made headway understanding genetic factors that may protect from AD. The biological implications and practical limitations of information gleaned from genome-wide association studies in AD over the years are also discussed. The readers will have an up-to-date understanding of where we are in our efforts to understand the layers of genetic complexity in AD.

Introduction

Alzheimer disease (AD) is a multifactorial, age-related neurodegenerative disease and the most common form of dementia. AD is clinically characterized by cognitive impairment that leads to progressive functional decline and neuropathologically characterized by amyloid-β extracellular plaques and hyperphosphorylated tau-containing intracellular neurofibrillary tangles (NFTs).[1] Over 6.7 million Americans older than 65 years are diagnosed with AD while 13.8 million are estimated to be affected by the year 2060 because of aging demographics.[2] While at least one Federal Drug Administration-approved disease-modifying therapy is now available, treatments that halt or reverse the disease remain elusive.[3,4]

While age is the greatest risk factor associated with AD and environmental factors are known to contribute to pathogenesis, the disease is highly heritable and discoveries made over the past 3 decades have begun to unravel the role that genetics plays in disease risk.[5-8] Early insights came in the late 1980s with the elucidation of genes associated with early-onset familial AD (EOFAD), establishing that a small proportion of AD in relatively young individuals has a monogenic etiology.[9,10] Subsequent advances in genomic technology enabled higher throughput studies of larger cohorts and identification of genetic contributions to complex disease. Genome-wide association studies (GWASs) of late-onset AD (LOAD), which accounts for the overwhelming majority of AD and is herein defined as polygenic AD afflicting those aged 65 or older, led to the detection of many more genetic variants—both deleterious and protective—that influence the risk of LOAD.[11] Thus, in contrast to EOFAD, the genetic architecture of LOAD has proven to be complex, with additional variants being continuously identified.[12]

Despite this progress, only a small fraction of the heritability of LOAD, which is measured to be between 58 and 79% by twin studies, is currently identifiable, making the determination of personalized risk difficult.[5,6] This problem is compounded by the lack of data derived from diverse populations. If the genetics of AD are poised to expand beyond the research setting and become a more prominent fixture in the clinic, more sophisticated polygenic risk scores (PRSs)

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Glossary

AD = Alzheimer disease; *APP* = amyloid precursor protein; ARIA = amyloid-related imaging abnormalities; EOFAD = early-onset familial AD; ER = endoplasmic reticulum; GWAS = genome-wide association studies; LOAD = late-onset AD; NFT = neurofibrillary tangle; OR = odds ratio; PLOSL = polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy; PRS = polygenic risk score.

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representative of all populations are needed. Furthermore, the biological relationship between GWAS-derived genetic loci and AD pathogenesis remains incompletely understood. While many loci have been identified, functional characterization of these implicated regions is needed. In this article, we will review the history of AD genetics and emerging concepts that aim to address these challenges in the future.

Autosomal Dominant AD

EOFAD comprises <1% of all AD caused by variants in amyloid precursor protein (*APP*), *PSEN1* (presenilin-1), and *PSEN2* (presenilin-2).[13] Unlike polygenic and oligogenic factors that contribute to LOAD, these 3 genes are nearly 100% penetrant.[14] EOFAD typically affects individuals harboring these variants at a younger age than LOAD and is designated EOFAD in such cases.[9] Despite early age at onset (AAO), most individuals without a clear autosomal dominant pattern of inheritance do not carry EOFAD gene variants.[15-17] Despite their rarity, studying monogenic EOFAD has provided invaluable pathologic insights into the causative biochemical mechanisms underlying AD. Indeed, the influential "Amyloid Hypothesis" was shaped by discoveries surrounding EOFAD, given that APP is cleaved into amyloid-β by an enzyme complex that requires either presenilin-1 or presenilin-2 for catalysis. Anti-amyloid immunotherapies—namely lecanemab, which has been reported to modestly slow cognitive decline in patients with AD—may support this hypothesis.[4] Longitudinal studies of EOFAD gene carriers have also illuminated the clinico-pathologic sequence patients typically experience.[18,19]

APP

Early clues into the genetic basis of EOFAD came from trisomy 21 studies. A biochemical study conducted in 1984 found that the amyloid isolated from an individual with trisomy 21 was identical to the amyloid-β that is a neuropathologic hallmark of AD, suggesting that—if amyloid-β was indeed a human protein—the corresponding gene may be located on chromosome 21.[20] By 1987, multiple groups isolated and cloned the *APP* gene, associating it with AD by genetic linkage studies.[20-22] While pathogenic point variants in *APP* causing Dutch hereditary cerebral amyloid angiopathy were known, the first AD-associated variant—the London variant (V717I)—was identified in 1991.[23,24] That same year, a second single-nucleotide substitution (V717F) named the Indiana variant was found. [23] To date, 66 *APP* variants have been proposed as disease causing.[25] *APP* variants are only responsible for 10–15% of EOFAD cases.[26] Many of these variants perturb the γ-secretase proteolytic site, increasing the ratio of amyloid-β-42/amyloid-β-40.[9,27] In addition to AD-inducing missense *APP* variants, a 2006 study found that duplications of the gene may also cause EOFAD.[28] Clinically, pathologic *APP* variants typically manifest with memory impairment in the 40s and 50s, following a similar course as LOAD.[29]

PSEN1 and *PSEN2*

In 1995, the AD3 locus on chromosome 14 was implicated in EOFAD and positional cloning studies identified multiple variants in *PSEN1*.[30] The same year, multiple familial AD kindreds originally from the Volga River region in Russia were found to carry a missense variant in *PSEN2* (N141I), a gene on chromosome 1 with greater than 60% homology to *PSEN1*.[31,32] The presenilins serve as one of the 4 subunits comprising the γ-secretase complex and are the essential catalytic component of this aspartyl protease, which cleaves, among other substrates, APP into amyloid-β.[33,34] *PSEN1* and *PSEN2* variants increase the amyloid-β-42/amyloid-β-40 ratio either through elevating amyloid-β-42 production, reducing amyloid-β-40 production, or both effects.[27,35] Complete loss-of-function variants in *PSEN1*—as well as other subunits of the γ-secretase complex including *PSENEN* and *NCSTN*—cause familial hidradenitis suppurativa, but not neurodegeneration.[36] However, variation within the promotor region of *NCSTN* has been shown to modify AD AAO in Volga German families.[37] *PSEN1* pathogenic variants comprise up to 70% of cases with >300 variants identified to date while AD associated with *PSEN2* variants is the rarest monogenic form of the disease.[25,26] EOFAD associated with *PSEN1* variants typically presents in the 30s–60s, although exceptions exist. For instance, aggressive variants, such as the L166P variant, may manifest in adolescence.[38] Patients with pathologic *PSEN2* variants have a later AAO in their 40s–70s and a disease duration that can be similar to LOAD.[39,40] In the prospective Dominantly Inherited Alzheimer Disease Network Observational Study, amnestic features are the most prominent presenting feature in EOFAD followed by other cognitive symptoms including aphasia and behavioral changes.[41] Nonmotor symptoms reported in these carriers include spastic paraparesis, myoclonus, generalized seizures, and neuropsychiatric manifestations including bipolar disorder and psychosis.[40,42-46]

APOE

Two missense variants define the *APOE* ε2 and ε4 alleles that are associated with strong protective and deleterious effects on AD risk, respectively.[47-50] The ε4 allele, which has an allele

frequency of 0.14 in the cognitively intact, remains the common variant conferring the greatest effect on AD risk with an odds ratio (OR) near 3.68 (95% CI 3.30–4.11) in a multiethnic meta-analysis.[51,52] The ε4 allele is also associated with a younger AAO in both sporadic and familial forms of the disease.[53-55] By contrast, the reference ε3 allele has an allele frequency of 0.79 in cognitively normal individuals while the least common ε2 allele has a frequency of 0.07 in the cognitively intact and is associated with a protective effect on AD risk with an OR near 0.62 (95% CI 0.46–0.85).[51,52] As reported by multiple studies, this mixture of protective and deleterious alleles leads to nonadditive genotype effects; relative to the common ε3/ε3 genotype, AD risk increases 2–4-fold for either the ε2/ε4 or ε3/ε4 genotypes, increases 9–15-fold for the ε4/ε4 genotype, and is approximately 40% reduced for either the ε2/ε3 and ε2/ε2 genotypes.[51,56-58]

While the association between ε4 and both AD risk and AAO has been known for over 25 years,[47-49] a complex relationship between *APOE* and the genetic architecture of AD is emerging. Illustrating this complexity, AD GWASs with and without adjustment or stratification for ε4 can give dramatically different effect size estimates for the same variant in the same data set.[59,60,e1] This can be particularly severe for rare variants. For example, rs569584007 near *API5* jumps from OR = 3.06 (95% CI 1.26–7.40; p = 0.013) to OR = 10.48 (95% CI 4.42–24.83; p = 8.8E-08) after *APOE* adjustment.[59] It can also mean the difference between nominal and genomewide significance for common variants. For instance, rs10498633 near *SLC24A4* is not associated with AD among ε4 carriers (OR = 0.96; 95% CI 0.90–1.03; p = 0.243) but has a much stronger signal among those without ε4 (OR = 0.87; 95% CI 0.82–0.92; p = 3.61E-07).[60] The strength of the association between ε2 and ε4 and AD risk or AAO varies with ancestry.[50,e2,e3] While ε4 is associated with increased AD risk across populations, albeit to different degrees, the protective effect of ε2 seems attenuated or inverted in non-European cohorts.[58,e2,e4-e6] Along these lines, a large 2023 study found that the ε4 allele is associated with an increase in AD risk among East Asians (OR = 4.54, 95% CI 3.99–5.17), non-Hispanic Whites (OR = 3.46, 95% CI 3.27–3.65), non-Hispanic Blacks (OR = 2.18, 95% CI 1.90–2.49), and Hispanics (OR = 1.90, 95% CI 1.65–2.18) to varying degrees while ε2 was not significantly associated with reduced AD risk in East Asian or Hispanic cohorts.[e6] While some of this difference is likely explained by environmental factors confounded with ancestry through race/ethnicity,[e7] there is evidence that local genetic variation plays a role. For example, local ancestry at *APOE* is associated with both AD risk and AAO.[e2] This difference may be explained by variation on the ε3 and ε4 haplotypes.[e2,e8,e9]

APOE influences AD risk through complex neurobiological mechanisms. Pathologic studies demonstrate that brains from individuals harboring the ε4 allele exhibit greater amyloid-β pathology.[51,e10,e11] Indeed, the clinical spectrum of AD risk conferred by the *APOE* genotype is reflected neuropathologically,

with amyloid-β plaque burden being lowest in ε2 carriers and highest in ε4 carriers.[e12] There are multiple candidate mechanisms to explain this correlation because ε4 is implicated in both impaired clearance/degradation and increased production of amyloid-β.[51,e13-e15] Beyond amyloid-β, ε4 has been suggested to promote tau aggregation and hyperphosphorylation, activate microglial-mediated neuroinflammation, contribute to synaptic dysfunction, and disrupt lipid metabolism.[51,e16-e22]

The advent of several disease-modifying therapies—namely aducanumab, lecanemab, and donanemab—has introduced new implications regarding AD genetic status.[3,4,e23] Specifically, multiple antiamyloid monoclonal antibody trials demonstrate an increased vulnerability to amyloid-related imaging abnormalities (ARIA) in *APOE* ε4 carriers.[3,e24] There is a spectrum of findings seen on neuroimaging that range from cerebral edema (ARIA-E) to hemosiderin deposition secondary to intracranial hemorrhages (ARIA-H).[e25] While patients are generally asymptomatic, ARIA can be associated with serious neurologic side effects.[e25] Moreover, the risk of developing ARIA shows clear gene dosage dependence (i.e., ε4 homozygotes have higher rates of ARIA than heterozygotes) while ε4 carriers experienced less benefit than noncarriers when treated with lecanemab.[3,4,e24,e26] Given the increased risk of ε4 carriers to morbidity of ARIA, determination of the *APOE* genotype has taken on a new level of clinical importance.

As *APOE* biology is further elucidated, strategies targeting *APOE* are being developed as an alternative to antiamyloid or antitau treatments.[e27] An important aspect of this endeavor is determining whether *APOE* ε4 increases AD risk by gain-of-function toxicity or merely by being less protective than ε2 or ε3.[e28] Given the multifaceted role *APOE* plays in the brain, both possibilities may be true depending on the mechanism in question.[e13-e19,e28-e30] Bypassing the intricacy of *APOE* biology, one approach would entail editing the *APOE* gene directly using CRISPR to convert ε4 to ε2 or ε3.[e27,e31,e32] Targeting the protein product of *APOE* ε4, another strategy is to neutralize apoE4 by generating antibodies selectively directed at the protein.[e28,e33-e35] Alternatively, several ways of mitigating the proposed pathologic effects of apoE4, such as reversing its hypolipidation by ABCA1 activation or altering its purportedly pathogenic conformation with small molecules, are also being pursued.[e28,e30,e36-e38]

SORL1

Unlike many AD risk genes first identified by GWASs, *SORL1* (sortilin-related receptor 1) was found by a targeted gene search of the endocytic pathway, which was hypothesized to modulate APP processing.[e39] Expression levels of the protein encoded by *SORL1* were also reduced in AD brain tissue, further implicating the gene.[e40] The 2007 study that linked *SORL1* to AD uncovered several SNPs in different ethnic populations, findings that were later reinforced when a

susceptibility locus including *SORL1* was implicated in a large GWAS.[e41] Subsequently, whole-exome sequencing of EOFAD pedigrees negative for *APP, PSEN1,* or *PSEN2* variants was found to harbor both missense and nonsense variants in *SORL1,* which were absent in ethnicity-matched controls.[e42] Larger exome studies have since revealed multiple coding variants in different *SORL1* domains with varying pathogenicity.[e43,e44] To date, most variants confidently termed causative for AD have been those leading to haploinsufficiency.[e45] Family studies where variants segregate with disease and are, therefore, more likely to be pathogenic have provided additional clues to putative mechanisms. For example, evaluation of an early-onset AD family with a heterozygous missense *SORL1* variant (R953C) revealed a severity of neuropathologic change reminiscent of *PSEN/APP* EOFAD, including cerebellar amyloid-β and TDP-43 LATE-NC pathology. The variant was found to alter SORL1 protein localization, retaining immature protein in the endoplasmic reticulum (ER), leading to abnormal maturation and impairment of SORL1 endosomal trafficking. Another *SORL1* variant (Y1816C) also segregates with AD in 3 unrelated families.[e46] Of interest, this variant does not impede SORL1 trafficking to the endosome but does impair SORL1 dimerization and sorting to the cell surface. The SORL1 protein is thus unable to engage with its binding partner, the multiprotein sorting assembly retromer, which disrupts normal endosomal recycling.[e46] These 2 examples underscore how variants in different SORL1 domains exert different pathogenic mechanisms. Another study surveying Caribbean Hispanics with either familial or LOAD found multiple exonic *SORL1* variants, including a common variant (minor allele frequency = 14.9%), within these cohorts.[e47] Furthermore, in the same study, transfected cells expressing these presumably pathogenic variants led to impaired APP endocytic processing, bolstering the claim that they are functionally relevant.[e47]

As more *SORL1* variants are found by exome sequencing and more families are screened for potential pathogenic variants, further classification of *SORL1* variants will be necessary. More than 600 rare variants have been documented.[e44,e48-e50] While truncating variants resulting in haploinsufficiency are considered causative for AD because they are not found in controls, some identified that ultra-rare missense variants may act as dominant negatives. In these cases, dominant negative variants may be even more pathogenic than haploinsufficiency variants, given that they also affect the remaining wild-type SORL1, thereby reducing functional levels by over half.[e51]

TREM2

Since the early 2000s, variants in the gene-encoding triggering receptor expressed on myeloid cells 2, *TREM2,* were known to cause polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL), an autosomal recessive neurodegenerative disease characterized by early-onset dementia and bone cysts.[e52] A PLOSL family reported in 1983 included individuals with "presenile" dementia, amyloid-β plaques, and NFTs, which prompted the authors to suggest a link between the etiology of PLOSL and AD.[e53] *TREM2* was definitively linked to AD in 2013 when multiple studies reported that the rare missense R46H variant conferred an OR ranging from 2.90 (95% CI 2.16–3.91) to 5.05 (95% CI 2.77–9.16)—considerably higher than ORs seen with any common AD risk variants and comparable with the *APOE* ε4 allele.[e54-e56] The penetrance of this variant has been disputed, with a 2014 study reporting a revised OR of 1.67 (95% CI 0.95–2.92), while a more recent meta-analysis measured the OR as 3.88 (95% CI 3.17–4.76).[e57,e58] Additional *TREM2* variants, such as R62H, have also been found to be pathogenic; however, many other candidate variants cannot be definitively associated with AD risk, given their rarity.[e57,e59] Through the identification of these rare variants, *TREM2* has also provided insight into biological mechanisms underlying AD pathogenesis beyond the "Amyloid Hypothesis." The protein encoded by *TREM2* is expressed on myeloid cells, most notably microglia—the innate immune cells of the CNS—which are implicated in the pathogenesis of AD.[e60] Given that the protein encoding *TREM2* is essential for microglial activation, AD-associated variants of the gene are proposed to induce microglial dysfunction that promotes AD pathology.[e61] While the original *TREM2* variants are not associated with increased AD risk in non-European populations, other variants, such as the L211P mutation (OR = 1.27, 95% CI 1.05–1.54) in African Americans or the H157Y mutation (OR = 11.01, 95% CI 1.38–88.05) in Han Chinese, have subsequently been identified.[e62,e63]

Common Variants in LOAD

There has long been interest in characterizing the heritable component of the more common form of AD, LOAD. Before the genomics era, clinical observations supported the notion of LOAD arising more often in select families despite the absence of clear Mendelian inheritance patterns.[13] For example, individuals with a first-degree relative with LOAD are at higher risk of disease and those with 2 parents with LOAD may have an even higher risk.[10,e64,e65] Like other highly prevalent, adult-onset diseases (e.g., hypertension, coronary artery disease, and diabetes mellitus) that lack a monogenic etiology, LOAD is a complex, polygenic disease defined by the aggregate risk conferred by many variants, each with a small effect size in isolation.[e66] The dramatic fall in price of genomic technologies, such as relatively inexpensive SNP arrays, in the late 2000s enabled the search for common, lower risk genetic variants that were uncovered by GWASs.[e66,e67] It is important to note that GWAS-identified variants do not imply biological relevance per se, only that the associated genomic region in proximity to the variant may be of pathophysiologic importance.[e67] Of note, this is true even with GWASs using whole-genome sequencing, given that functional characterization of variants of undetermined pathogenicity is necessary regardless of degree of coverage.[e67]

The first AD-focused GWAS was conducted in 2007 and, being limited to 1,086 participants (664 AD cases and 422 controls), only implicated the *APOE* locus.[e68] Since then, over 100 independent variants across over 80 AD susceptibility loci have been nominated through ever larger GWAS, the most recent including over 1.1 million individuals.[12,e69] To reach these sample sizes, most recent AD GWASs include "cases" who are diagnosed clinically rather than confirmed by biomarkers or autopsy or even "proxy" cases with only a positive family history of dementia. The effect sizes associated with most of these common variants (minor allele frequency >5%) are relatively modest, with ORs ranging between 1.05 and 1.25.[e70,e71] In addition, while many susceptibility loci are not yet firmly linked to specific causative genes, functional genomic analyses have identified variants in a number of genes that reside in AD loci, strengthening the case for their potential roles in pathogenesis.[e70,e71] Thus, while the current understanding of the genetic architecture of LOAD does not yet explain heritability to a degree that would be clinically useful, such as for diagnosis, the growing list of causative genes has furthered understanding of disease-relevant biological processes. For instance, within GWAS-identified susceptibility loci, there is an enrichment of genes involved in pathways including amyloid-β and tau aggregation, endocytosis/phagocytosis, neuroinflammation, and lipid metabolism.[12] The Table organizes a selection of genes detailed in this work into these pathways. While these insights are intriguing and have opened new avenues of research, more functional studies are required to fully explicate how the growing number of AD risk genes and their implicated pathways interplay to drive AD pathogenesis.

Finally, like many early *APOE*-associated AD risk studies, research into common variants by GWASs has neglected non-European populations.[e72] Given that GWAS ORs are calculated by comparing the relative SNP frequency in disease and control groups and that SNP frequencies are significantly different across ethnicities, most of the available results may not generalize to non-Europeans.[e67] More diverse data sets are required to overcome this significant limitation, which is an additional barrier to clinical application. Furthermore, studying risk in underrepresented ethnicities provides opportunities to discover new genetic loci that may provide additional clues to disease pathogenesis.[e73]

Rare Variants in LOAD

Despite the growing number of identified AD susceptibility loci, only a minority fraction of heritability—3.1% per the largest study to date—is explained by GWAS-derived data.[e69] The heritability of LOAD is estimated to be between 58 and 79% as measured by twin studies, implying considerable missing heritability.[5,6] A portion of this hidden fraction may be accounted for by rare (i.e., minor allele frequency <1%) coding variants, which were not regularly searched before advances in sequencing technologies allowed implicated genes to be routinely sequenced.[e74] Through this approach, an expanding list of deleterious rare coding variants—most

notably in *TREM2*, *SORL1*, and *ABCA7*—have been uncovered.[11,e75] Despite this progress, rare variants remain underexplored as a source of missing heritability.[e74]

Common variants in the adenosine triphosphate-binding cassette subfamily A member 7 gene (*ABCA7*) were first implicated through a GWAS in 2011.[e76] A subsequent study leveraged whole-genome data from an Icelandic population to identify rare, loss-of-function variants in *ABCA7* conferring an OR of 2.12 ($p = 2.2 \times 10^{-13}$), findings that replicated in European and American cohorts (OR = 2.03, $p = 6.8 \times 10^{-15}$).[e77] Another study using next-generation sequencing of *ABCA7* exons, introns, and regulatory sequences detected an increase in loss-of-function variants in patients with AD compared with healthy controls (relative risk = 4.03, 95% CI 1.75–9.29).[e78] As with *SORL1*, premature termination codon variants confer moderate-to-high penetrance.[e79] Although further studies are needed in diverse populations, exome sequencing of an African American cohort revealed 2 *ABCA7* missense variants, rs3764647 (OR = 1.47, $p = 0.018$) and rs3752239 (OR = 4.65, $p = 0.047$), which confer AD risk.[e80] The precise pathogenic mechanism of *ABCA7* remains unknown, but dysregulated lipid metabolism, mislocalization from the plasma membrane to the ER, and reduced microglia-mediated amyloid-β clearance are possibilities.[e81,e82]

Although less studied than *TREM2*, *SORL1*, and *ABCA7*, rare variants in additional genes have been implicated in AD, many with evidence of functional relevance providing insight into potential disease mechanisms. For example, proteins encoded by rare variants in the extracellular chaperone gene, *CLU* (clusterin), the first AD risk gene to be detected by 2 independent GWASs, are not properly secreted, impairing its putative role in amyloid-β clearance through the endocytic pathway.[e70,e83] A 3-base pair insertion in the gene encoding bridging integrator 1 (*BIN1*), which is associated with elevated risk of AD (OR = 1.20, 95% CI 1.14–1.26), is associated with increased transcriptional activity in vitro and expression within the human brain.[e84] *BIN1* undergoes extensive tissue-dependent differential splicing, with brain isoforms including exons important for endocytosis and intracellular trafficking.[e85] Variants in the AD risk gene, *CR1* (complement C3b/C4b receptor 1), which plays a role in innate immunity, are believed to potentially alter activation of the complement cascade.[e86]

Variants, both rare and common, with purported functional impact are also reported in *ADAM10*, *APH1B*, *CCDC6*, *CD2AP*, *FERMT2*, *GRN*, *IL34*, *INPP5D*, *LILRB2*, *MS4A6A*, *NCK2*, *NME8*, *PICALM*, *PILRA*, *SHARPIN*, *TMEM106B*, *TNIP1*, *TSPAN14*, *UNC5C*, and *UNC5CL*, among others.[13,e44,e69,e71,e87-e89] As more extensive sequencing of ever larger cohorts is undertaken, functional variants in additional genes initially implicated by GWASs or candidate gene studies will continue to be delineated. In addition to partially addressing the remainder of missing AD heritability, the diversity of implicated genes may reveal novel therapeutic strategies.

Table Summary of Genes Discussed With Corresponding Biological Pathways Implicated in the Pathogenesis of AD

Gene	Chromosomal location	AD type	Implicated pathway[e87,e122]
APP[a]	21q21.3	EOFAD	APP metabolism, neuroinflammation[9,27]
PSEN1	14q24.2	EOFAD	APP metabolism[9,27]
PSEN2	1q42.13	EOFAD	APP metabolism[9,27]
APOE[a]	19q13.32	LOAD	APP metabolism, tau pathology, lipid metabolism, neuroinflammation, neurotransmission[51]
SORL1[a]	11q24.1	EOFAD/ LOAD	APP metabolism, tau pathology, endolysosomal[e40]
TREM2	6p21.1	LOAD	APP metabolism, tau pathology, neuroinflammation, lipid metabolism[e61]
ABCA7[a]	19p13.3	LOAD	APP metabolism, neuroinflammation, lipid metabolism[e82,e123]
CLU	8p21.2	LOAD	APP metabolism, tau pathology, neuroinflammation, endolysosomal, neurotransmission[e83]
BIN1	2q14.3	LOAD	Endolysosomal, neurotransmission[e84]
CR1	1q32.2	LOAD	Neuroinflammation[e86]
PLCG2[a]	16q24.1	LOAD	Neuroinflammation, endolysosomal[e98]
ADAM10	15q21.3	LOAD	APP metabolism[e124,e125]
APH1B	15q22.2	LOAD	APP metabolism[e126]
CCDC6	10q21.2	LOAD	Unknown
CD2AP	6p12.3	LOAD	APP metabolism, tau pathology, endolysosomal, neurotransmission[e127]
FERMT2	14q22.1	LOAD	APP metabolism, neurotransmission[e128]
GRN	17q21.31	LOAD	Neuroinflammation, endolysosomal[e129]
IL34	16p22.1	LOAD	Neuroinflammation[e130]
INPP5D[a]	2q37.1	LOAD	Neuroinflammation, endolysosomal[e131]
LILRB2	19q13.42	LOAD	APP metabolism, neuroinflammation[e132]
MS4A6A[a]	11q12.1	LOAD	Neuroinflammation[e133]
NCK2	2q12.2	LOAD	Neuroinflammation[e134]
NME8[a]	7p14.1	LOAD	Axonal transport[e135]
PICALM[a]	11q14.2	LOAD	APP metabolism, tau pathology, endolysosomal[e136]
PILRA[a]	7q22.1	LOAD	Neuroinflammation[e137]
SHARPIN	8q24.3	LOAD	Neuroinflammation (TNFα), neurotransmission[e138]
TMEM106B[a]	7p21.3	LOAD	Endolysosomal[e139]
TNIP1[a]	5q33.1	LOAD	Neuroinflammation (TNFα)[e140]
TSPAN14[a]	10q23.33	LOAD	APP metabolism, neuroinflammation[e141]
UNC5C	4q23	LOAD	Neuronal apoptosis[e142]
UNC5CL	6p21.1	LOAD	Tau pathology[e143]
RELN[a]	7q22.1	N/A	Tau pathology[e101]
CCL11[a]	17q21.1	N/A	Neuroinflammation[e104]

[a] Genes that are associated with protective variants.

Protective Variants in AD

Progress has also been made into uncovering protective variants. As mentioned previously, the *APOE* ε2 allele reduces risk of AD by approximately 40% and partially mitigates the increased risk conferred by the ε4 allele. Similarly, *KL*, an extensively studied longevity gene encoding the α-klotho protein, negates the deleterious impact of ε4 allele when both are present.[e90,e91]

Specifically, the *KL-VS* variant, which is a functional haplotype defined by 2 missense variants (F352V and C370S), was associated with reduced AD risk (hazard ratio = 0.69, 95% CI 0.61–79), higher levels of amyloid-β in CSF, and lower levels of amyloid-β on PET imaging in individuals aged 60–80 years who were heterozygous for *KL-VS* and *APOE* ε4.[e91] KL is proposed to be involved in a wide range of signaling pathways (e.g., insulin-like growth factor 1, Wnt, and hypoxia-inducible factor signaling) and cellular functions including vitamin D/phosphate metabolism, apoptosis, and autophagy.[e92,e93] While the precise mechanism by which *KL-VS* is protective in ε4 carriers is unknown, α-klotho may promote amyloid-β clearance by enhancing autophagy.[e93-e95] *KL* is expressed predominantly in choroid plexus, parathyroid glands, and renal tissue but can be cleaved to become a soluble protein, suggesting that its effects may be mediated through a hormonal mechanism.[e92,e93] Genes better known for their AD-inducing pathogenic variants also have protective variants. For example, the *APP* A673T mutation, a rare variant found in an Icelandic cohort that is nearly absent from non-Nordic populations, is associated with an OR near 0.24 ($p = 4.19 \times 10^{-5}$).[e96,e97] This variant is near the β-cleavage site of APP and resulted in a 40% reduction in amyloidogenic fragments in vitro.[e96] Protective variants have been found in other genes, including *SORL1*, *ABCA7*, and *PLCG2*, among others.[e98-e100] Of note, protective *SORL1* alleles, while ultimately present in both Japanese and Caucasian cohorts, were only first detected on evaluation of a Japanese cohort, given a much higher frequency, underscoring the benefit of studying non-European populations.[e100]

A recent development is the detection of rare variants that may confer "extreme resilience" to AD, conferring high degrees of protection in individuals harboring an EOFAD gene, a cohort that would be expected to invariably become symptomatic.[e101] To date, 2 such rare variants have been identified: the *APOE* Christchurch variant (R136S) and a purported gain-of-function missense mutation in *RELN* (reelin), known as the RELN-COLBOS variant (H3447R).[e101,e102] Discovered in 1987, the Christchurch variant was initially associated with hyperlipidemia; however, a 2019 study reported that an individual from a large Colombian kindred homozygous for this variant and positive for the *PSEN1* E280A mutation, which typically induces symptomatic onset in the 40s, did not develop mild cognitive impairment (MCI) until her 70s.[e102,e103] This individual exhibited limited tau pathology despite a high burden of amyloid-β plaques.[e102] Similarly, in 2023, an individual harboring a *PSEN1* E280A mutation who was not diagnosed with MCI until age 70 was found to be heterozygous for the RELN-COLBOS variant.[e101] Of interest, this individual displayed both amyloid-β and tau neuropathology on autopsy; however, the entorhinal cortex was conspicuously spared of tau pathology.[e101,e102] Furthermore, a missense mutation in *CCL11*, a gene encoding the chemokine eotaxin-1, delayed symptomatic onset by approximately 10 years in the *PSEN1* E280A cohort.[e104] Although exciting for their potential therapeutic implications, these reports require further validation, given their inherently small sample size, to determine the effects in the context of other *PSEN1*, *PSEN2*, and *APP* variants.

These examples of "extreme resilience," which all originate from the same Colombian kindred, are a testament to the benefits of studying non-European populations. Indeed, an alternative strategy to uncover protective variants that would otherwise go undetected may entail searching for pedigrees with unique genetic admixtures that are not currently captured in available data sets.[e73]

Polygenic Risk Scores in AD

Large GWASs in the 2010s revealed the polygenicity of AD using dozens of AD risk variants, leading to efforts to develop PRSs for clinical and research applications. A long-term goal of PRSs is to accurately capture the personalized risk of an individual in a clinically relevant manner.[e105] While progress has been made, PRSs generally do not currently perform well with either prediction of individual risk or population screening because of a host of factors including relative lack of data collected from non-European populations and difficulty interpreting results in the context of personalized lifetime risk.[e106,e107]

Using GWAS data, efforts in the 2010s sought correlations between PRSs and AD phenotypes, such as neuroimaging biomarkers.[e108,e109] A 2017 study developed a polygenic hazard score (PHS) demonstrating that individuals in the top quartile had a higher AD incidence and lower AAO.[e110] Indeed, the difference in symptomatic onset between the top and bottom decile was greater than 10 years in *APOE* ε3 homozygotes.[e110] This study also found associations between higher scores and various AD neuropathologic hallmarks (i.e., degree of amyloid-β plaque, NFTs, and hippocampal atrophy).[e110] A follow-up study systematically evaluated association of 8 cerebral regions of interest, finding that the PHS was predictive of significantly greater postmortem level of amyloid-β plaques and NFTs in all areas.[e111]

An important factor influencing the predictive power and utility of PRSs is the unique role *APOE* plays in AD genetic architecture, given the outsized effect the gene has on AD risk. For example, a 2023 prospective study found that a PRS excluding *APOE* was no better at predicting AD than *APOE* alone.[e112] In addition, a study conducted in 2021 using a PRS consisting of 82 SNPs (excluding *APOE*) implicated in AD risk was only slightly better at predicting disease when compared with simple factors such as age, sex, and *APOE* status.[e87] However, the wide phenotypic spectrum among *APOE* ε4 homozygotes suggests that the remaining polygenic component of AD risk may account for some of this diversity. Relatedly, a study comparing cognitively normal and demented *APOE* ε4 homozygotes found a significantly higher PRS in patients with AD, suggesting that genetic factors beyond *APOE* modify disease risk in this cohort.[e113]

A related method to traditional PRSs is pathway PRSs, which are especially useful in defining risk of specific biological processes. While traditional PRSs attempt to determine

Figure Schematic of Interrelated Biological Pathways and Their Comprising Genes in the Context of AD Pathogenesis (in eReferences e87 and e122)

Known processes contributing to AD pathogenesis are represented with red arrows and boxes. Pathologic processes that may exacerbate AD pathogenesis but that are also associated with aging more generally are shown in boxes with gray background. Potential relationships between pathways that are relatively less well understood and may provide new avenues into understanding the genetics of AD risk are shown as dashed arrows. Created in BioRender. Jayadev, S. (2024) BioRender.com/q00h227. AD = Alzheimer disease.

disease risk by summing all the identified phenotype-relevant risk alleles weighted by their respective effect size estimates, pathway PRSs selectively integrate variants affecting a specific biological pathway.[e105,e114] Thus, although traditional PRSs may help to ascertain overall risk of developing disease, pathway PRSs may be superior in predicting specific biomarkers of pathology, such as amyloid-β deposition in the context of AD.[e114-e117] Moreover, pathway PRSs may enable a more personalized approach by identifying biological pathways that contribute to AD risk and pathogenesis to a greater degree in some individuals rather than others. As with the genetics of AD more broadly, PRS development has neglected non-European populations.[e118] In addition to representing a conspicuous gap in knowledge, this reality has the potential to exacerbate health disparities that already exist.[e119]

Conclusion

Since the early discoveries into the monogenic causes of EOFAD to the growing list of common and rare variants shaping AD risk, the field of AD genetics is entering a new period of discovery and growth. Advances in the throughput of sequencing technologies are enabling larger and high-quality data sets, which will hopefully continue to expand understanding of the complex genetic architecture of this disease. Relatedly, the ongoing identification of additional AD risk genes continues to expand the understanding of AD pathogenesis beyond just APP metabolism, as shown in the Figure. Furthermore, long-read sequencing techniques, including nanopore sequencing and single-molecule real-time sequencing, are capable of reads measured in kilobases, allowing lengthy repetitive regions to be fully resolved.[e120] Such an improvement may have direct application to the problem of missing heritability in AD, given that large structural variations (e.g., deletions, duplications, and insertions), which are predicted to contribute to AD risk, are difficult to detect by older sequencing technologies.[e121] Ultimately, further research is needed to identify the missing heritability of AD, characterize the AD genetics of non-European populations, improve the accuracy of PRSs for clinical application, and continue to elucidate the aspects of AD pathogenesis that remain incompletely understood.

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