REVIEW ARTICLE

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Genetics of Alzheimer Disease

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ABSTRACT

PURPOSE OF REVIEW: **This article discusses the spectrum of genetic risk in familial and sporadic forms of early- and late-onset Alzheimer disease (AD). Recent work illuminating the complex genetic architecture of AD is discussed in the context of high and low risk and what is known in different populations.**

RECENT FINDINGS: **A small proportion of AD is autosomal dominant familial AD caused by variants in *PSEN1, PSEN2,* or *APP*, although more recently described rare genetic changes can also increase risk substantially over the general population, with odds ratios estimated at 2 to 4. *APOE* remains the strongest genetic risk factor for late-onset AD, and understanding the biology of *APOE* has yielded mechanistic insights and leads for therapeutic interventions. Genome-wide studies enabled by rapidly developing technologic advances in sequencing have identified numerous risk factors that have a low impact on risk but are widely shared throughout the population and involve a repertoire of cell pathways, again shining light on potential paths to intervention. Population studies aimed at defining and stratifying genetic AD risk have been informative, although they are not yet widely applicable clinically because the studies were not performed in people with diverse ancestry and ethnicity and thus population-wide data are lacking.**

SUMMARY: **The value of genetic information to practitioners in the clinic is distinct from information sought by researchers looking to identify novel therapeutic targets. It is possible to envision a future in which genetic stratification joins other biomarkers to facilitate therapeutic choices and inform prognosis. Genetics already has transformed our understanding of AD pathogenesis and will, no doubt, continue to reveal the complexity of brain biology in health and disease.**

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INTRODUCTION

Alzheimer disease (AD) is the most common cause of dementia in the United States, and age is the greatest risk factor in late-onset sporadic AD. However, genetic factors are key contributors to all forms of AD, both early onset and late onset. A range of genetic risk exists for developing AD. The rare familial forms of AD caused by single-gene variants (mendelian AD) were recognized decades ago; these are families in which AD typically occurs early and in every generation. Most AD is

not so predetermined, although we know genetic factors exist that increase the risk for typical late-onset AD and sporadic early-onset AD (onset at younger than 65 years of age). The known genetic variants can cause nearly 100% fully penetrant disease, as in the case of rare autosomal dominant early-onset familial AD, which comprises less than 1% of all AD; increase risk by a few times compared to the general population; or, in the case of common polymorphic variants, contribute to AD risk as an aggregate load of risk alleles (ie, form of a gene). Understanding the impact of AD genetic risk is important when discussing lifetime chance of developing the disease and implications to family members. A common question is "My mother has Alzheimer disease and so did her mother. Am I going to get it too?"

Late-onset sporadic AD is highly heritable, estimated at 60% to 80%.[1] Those nonmendelian but heritable factors include common low-risk variants and rare but higher-risk gene variants.[2] One goal of future "precision" therapies in neurodegenerative disease is to leverage knowledge of genomics and biological processes to link the "right" person with the "right" drug. AD trials specifically targeted at carriers of mendelian forms of early-onset familial AD are now under way, and the apolipoprotein E (*APOE*) genotype is being considered in some ongoing trials for late-onset AD. Large-scale genomic studies in late-onset sporadic AD have identified numerous genetic AD risk variants representing a spectrum of biological pathways driving AD pathogenesis. It is possible therefore that an individual's profile of common genetic risk factors may be considered when choosing a particular drug targeting a pathway relevant to the patient's underlying disease mechanism(s).[3] Although not yet ready for clinical use, in the future, AD diagnosis, prognostication, and treatment may be refined with the guidance of genetics.

The field of AD genetics is expanding rapidly, and this article may not capture all of the emerging AD risk gene candidates. Nevertheless, it will serve as a framework to understand the multifaceted influence of genetic risk. The search for AD genes began with linkage analysis studies in families in the early 1990s, in which researchers could capitalize on the link between a disease and chromosomal location to identify a region of interest in the genome, then sequence nucleotide by nucleotide to identify gene mutations. Sequencing in this manner was limited by time and cost; thus, it was useful for small cohorts or families but not applicable on a larger population level. In the clinic, individuals with clearly mendelian and stereotypical versions of well-characterized diseases could be offered single-gene testing, although usually at prohibitively high costs if not covered by insurance. The advent of next-generation sequencing transformed the ability to bring genetic testing to the clinic and expanded the capacity to search for genetic variants in the population at large, beyond the rare families that are ascertained because of disease severity or penetrance.[4]

This article discusses AD genetics as the history of genomic discovery has unfolded over the years, beginning with a discussion of the early-onset single-gene-variant autosomal dominant forms of disease and the discovery of *APOE*. Although a formal definition of "early-onset" AD has not been established, it is typically considered as an age of onset younger than 65 years. Next, the article takes a high-level view of additive and polygenic risk attributed to sporadic late-onset AD. The current state of knowledge of common low-impact genetic variants that contribute to AD risk is described, and the more recently identified genetic factors that appear to confer a significant, but incomplete, risk for AD

KEY POINT

- **Rare single-gene causes of Alzheimer disease (AD) exist, although even sporadic AD likely has important genetic contributions.**

and are generally rare in the general population are reviewed. The article also briefly reviews the state of clinical genetic testing and comments on the current and future efforts necessary for complete health care equity.

AUTOSOMAL DOMINANT ALZHEIMER DISEASE

Families with multiple generations of early-onset AD were followed for many decades by clinicians and investigators convinced of a single genetic driver underlying their dramatic AD presentations. In the 1990s, after collecting DNA samples from a number of such families, researchers used genetic linkage and sequencing to identify pathogenic variants in three genes, presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), and amyloid beta precursor protein (*APP*), which led to near completely penetrant AD.[5-7] Shortly afterward, it was found that the protein products of these three genes were also biologically related to amyloid plaques, one of the neuropathologic hallmarks of all forms of AD. *PSEN1* and *PSEN2* protein products are the enzymatic subunit of the γ-secretase complex, which cleaves APP, resulting in amyloid-β (Aβ) peptide. Families with *APP, PSEN1*, and *PSEN2* variants are rare, onset is typically at an earlier age, and the gene variants nearly always cause disease. In total, variants in these three genes explain a portion of early-onset familial AD. *PSEN1* variants are most common, comprising 50% to 75% of all early-onset familial AD; *APP* variants comprise 10% to 15%, and *PSEN2* variants are rarer, found in approximately 5% to 7% of patients with early-onset familial AD.[8]

Pathologically, the autosomal dominant forms have similar findings to late-onset AD, namely Aβ plaques and neurofibrillary tangles, although the early-onset familial AD forms can have more impressive pathology at the time of autopsy.[9] Given the clinical and pathologic similarities, autosomal dominant AD has served as a framework for AD pathogenesis. Individuals who have inherited a disease-causing gene variant are destined to develop the disease, thus biomarkers obtained before clinical onset are valuable to track early biological changes before clinical disease appears. Studies in families with autosomal dominant AD have been extremely valuable, allowing the temporal tracking and relative positioning of each biomarker to the other over the course of time, including the period before disease onset, building the developing understanding of AD pathophysiology.[9]

APP

APP was the first of the three autosomal dominant AD genes to be discovered. In 1991, investigators reported the *APP* V717I (London) variant found in an English kindred, with an average age at onset in the midfifties.[7] In the same year, a group in the United States reported another variant at the same position, the *APP* V717F (Indiana) variant, with an associated age of onset in the midforties.[10] APP had already been implicated as the precursor protein cleaved to generate the Aβ peptide found in plaques[11,12] as well as the genetic cause of hereditary cerebral hemorrhage with amyloidosis–Dutch type.[13] Individuals with Down syndrome (trisomy 21) have an extra chromosome 21 and consequently three alleles of *APP*. In 1984, Glenner and Wong[14] demonstrated that the amyloid pathology found in individuals with Down syndrome was biochemically identical to the amyloid protein found in AD, creating a genetic link between APP and amyloid plaque. Clinically, *APP* variants lead to short-term memory loss, with a range of age onset in the forties to fifties.[10] There are more than 50 pathogenic variants in *APP*

associated with AD, most of which fall within or near the region cleaved by the secretase complexes to release Aβ peptide, although it should be noted that duplications of *APP* in families with early-onset familial AD have also been reported.[2,8] Typically, missense mutations disrupt normal proteolytic APP cleavage, leading to alteration of the size of cleaved amyloid peptide product and a relative increase of the Aβ42 forms.[15] Because of this, variants such as the Swedish *APP* mutation are commonly used in AD genetic animal models to drive excessive Aβ production aiming to mimic the human AD neuropathologic state.

PSEN1 and *PSEN2*

The clinical features of *PSEN1* and *PSEN2* variants overall are similar to that of sporadic AD, typically beginning with progressive memory-predominant cognitive decline. The striking distinction between *PSEN*-variant AD and sporadic AD is the early age of onset which, in the case of some *PSEN1* variants, can be in the late twenties. In general, the range of onset of *PSEN1* is broad, from the thirties to sixties and, rarely, the late seventies. Although nearly all individuals who carry a pathogenic *PSEN1* variant develop disease, meaning the variants are completely penetrant, rare "escapees" have been reported.[16-18] Generations of families with early-onset autosomal dominant AD who were found to trace their ancestry to the Volga River region of Russia led to the identification of the *PSEN2* N141I allele, the Volga German variant, and *PSEN2* as an autosomal dominant AD gene.[6] *PSEN2* variant age of onset range is later, typically in the forties to seventies, with evidence of decreased penetrance compared to *PSEN1*. The disease duration can be somewhat shorter in certain families with *PSEN1* variants, and families with *PSEN2* variants have, on average, a duration similar to sporadic AD.[19] A general trend of age of onset specific to each variant is seen, allowing for gross prediction of age of onset for research purposes.[9] More than 200 pathogenic variants have been identified in *PSEN1* and 15 in *PSEN2*.[8] Although much clinical overlap exists between *PSEN* AD and sporadic AD, several variants are associated with less common neurologic features, such as spastic paraparesis, myoclonus, pyramidal signs, cerebellar signs, and behavioral disturbances.[20] Seizure is not uncommon, and both *PSEN1* and *PSEN2* pathogenic variant carriers have a higher risk of seizure than the general population.[19,21,22]

Rarely, an autosomal dominant AD variant has not been inherited from either parent but rather arose spontaneously in the affected person, which is termed *de novo*.[23,24] Detection of somatic mosaicism, in which not all tissues of an individual carry the disease variant, therefore leading to gene variant expression in the brain (but not in blood, making blood testing uninformative), is difficult in the clinical setting. Work is ongoing to evaluate the possibility that mosaicism may contribute to the risk of sporadic AD, although, as yet, few reports have documented this phenomenon.[25]

APOE

The initial discovery of the rare autosomal dominant AD genes explained some, but by no means all, of the original AD multigenerational families. In 1993, a series of studies reported the identification of the ε4 allele of the *APOE* gene as a risk factor for both familial AD and sporadic AD.[26-28] Since that time, *APOE* ε4 has attracted researchers keen to leverage the knowledge of a genetic factor that still, 30 years later, has the highest odds ratio of any common gene variant.

KEY POINTS

- Early-onset autosomal dominant familial AD can be caused by variants in the *PSEN1*, *PSEN2*, and *APP* genes.
- *PSEN1* variants are the most common autosomal dominant form of AD.
- Individuals with Down syndrome have three copies of the *APP* gene and can also present with AD-type dementia and neuropathology.
- Significant clinical overlap exists between *PSEN*-related AD and sporadic AD, although patients with *PSEN*-related AD may develop spasticity, movement disorders, and cerebellar signs.
- *APOE* is the strongest known genetic risk factor for typical late-onset AD.

Polymorphisms at two residues in *APOE* give rise to three alleles: *APOE* ε2; *APOE* ε3, the most common allele; and *APOE* ε4, which increases risk for AD by twofold to threefold. Being homozygous (ie, carrying two *APOE* ε4 alleles) is associated with an odds ratio of 12 compared to those with two *APOE* ε3 alleles, whereas *APOE* ε2/ε2 homozygotes have a markedly decreased risk of AD, with an odds ratio of 0.6.[29] The *APOE* ε4 allele lowers age of onset in both mendelian and sporadic forms of AD.[30-32] Notably, the effect of *APOE* ε4 on risk appears to be less relevant in older ages.[33] Although *APOE* ε4 AD is not clinically distinct from sporadic AD,[34,35] recent work comparing *APOE* ε4 frequency in subtypes of AD shows a higher association with memory-prominent (amnestic) AD.[36] Conversely, the *APOE* ε2 allele is correlated to lower risk of AD.[29]

Many of the initial genetic studies assessing *APOE* ε4 risk, including those mentioned above, were conducted in non-Hispanic White populations. However, it soon became apparent that variability in estimated risk was associated with *APOE* ε4 not just by age but also by ancestry and race. Of note, the frequency of *APOE* ε4 differs between populations.[37] Multiethnic studies revealed that the elevated risk of *APOE* ε4 is weaker in African American and Hispanic cohorts and stronger in Japanese individuals.[38,39] Furthermore, differences in *APOE* ε4 risk across populations has been related to the ancestral origins of the local chromosomal region containing the *APOE* ε4 allele in an individual.[37] This unraveling field of known AD genetic risk factors in the context of population backgrounds is a critical step in the development of *APOE*-related therapies that can be broadly applicable to communities.

COMMON GENETIC RISKS IN LATE-ONSET ALZHEIMER DISEASE

Identifying genetic factors that contribute to complex disease is an opportunity to clarify risk and tease apart biological contributions to disease pathogenesis. Common sporadic adult-onset diseases, such as late-onset AD, diabetes mellitus, coronary vascular disease, and hypertension, typically lack a single genetic factor that drives risk. However, the evidence that these traits sometimes appear more often in some families than others speaks to the presence of low-risk gene variants that, in aggregate, tip the scales toward disease.[40] Before the ability to systematically search for genetic contributions to late or nonmendelian AD, accumulating patient data strongly supported the presence of as-yet unidentified genetic factors.[41] Children of conjugal pairs of individuals with late-onset AD (both mother and father with nonmendelian late-onset AD) appear to have a higher risk of developing AD themselves,[42,43] and having a first-degree relative with AD also increases risk.[44,45] In addition, more recent data suggest that having a second- or third-degree relative with AD may be associated with a higher-than-expected risk for AD.[46]

As discussed above, the work to find genetic contributors to more common late-onset AD was bolstered by technologic advances. Ideally, one would sequence the whole genome of a population on a large enough scale to assess how common genetic risk can cause a common disease. This objective remains conceivable, although not yet feasible. Almost 20 years ago, researchers reported the first genome-wide association studies, which identify associations between a biological trait and genetic variants.[47] In this analysis, regions of DNA are identified by a particular single-nucleotide polymorphism (SNP), and thus the entire genome can be queried through hundreds of thousands of SNPs on an array to determine if one SNP allele (eg, a C or T) is more associated with disease than

another. Once a region has been identified as significantly associated with disease, the genes within that region can be more thoughtfully queried for their potential relationship to disease. Thus, genome-wide association studies allowed for high-throughput large-scale scanning across the genome to begin to unravel common genetic variations and their relationship to diseases such as late-onset AD.

Numerous genes have been implicated through genome-wide association studies since the first study in 2007.[48] Replication is a key criterion when evaluating genome-wide association study "hits," and recent meta-analyses and larger-scale studies have nominated at least 40 genes that are likely relevant to AD.[49-53] Of note, after being identified through genome-wide association studies, sequencing of the coding regions of some of these genome-wide association study–identified genes, such as *ABCA7*, *BIN1*, and *CLU*, has identified rare variants in those genes that further support their pathogenicity. Caveats exist to the use of genome-wide association studies, including the constraint that genome-wide association studies only reveal the genomic region significantly associated with disease but do not directly point to which of the many genes in that region are involved. A huge limitation to genome-wide association study data currently is the relative lack of studies in people other than the non-Hispanic White population. Because genome-wide association studies estimate odds ratios based upon the relative frequency of a SNP in a disease cohort versus control, it matters that SNP frequencies differ among control cohorts from various ancestries. Polygenic risk scores are based on the premise that aggregate risk can be tallied and scored to yield one value summarizing an individual's disease risk and are therefore not widely applicable at this time given the limitations to applicability in the general public.

The vast majority of SNPs interrogated by genome-wide association studies are noncoding, thus additional functional genomic studies or analyses are needed to extract more specific information about what is driving the disease signal. Additionally, even SNPs that are replicated and are genome-wide significant confer a modest effect on disease risk. To date, the odds ratios associated with the top replicated late-onset AD common variants are low, typically 1.1 to 1.3.[2] However, it should be noted that individuals who comprised the genome-wide association study datasets were ascertained at various times and at various stages of disease and were not all pathologically confirmed cases of AD. Thus, it is possible that some positive signals may be diluted. Nevertheless, the current utility of genome-wide association studies is realized in understanding relevant genes contributing to pathogenesis rather than for prediction of disease risk in the clinic.[54] A number of exciting biological insights have been revealed through genome-wide association studies that may have future potential to inform therapeutic development. Pathways implicated by genome-wide association studies include expected mechanisms, such as APP processing and tau, but also a wider spectrum of neuronal and non-neuronal functions, including lipid processing, endolysosomal processing, and immune biology.[53,55]

RARE VARIANT ALZHEIMER DISEASE

Genome-wide association studies have been successful in identifying components of the complex genetic architecture that contributes to late-onset AD in the general population. By design, the studies were conducted using genetic variants that are common in the population (occurring in more than 1% of the population) to identify regions of the genome that were associated with

KEY POINTS

- ***APOE*** **has three isoforms, *APOE* ε2, *APOE* ε3, and *APOE* ε4, and *APOE* ε3 is the most common allele.**
- ***APOE*** **ε4 confers the highest risk for AD.**
- ***APOE*** **ε4 associated risk varies between populations of different ancestries.**
- **Genome-wide association studies identify associations between a disease trait and a common genetic variant.**
- **Polygenic risk scores are generated based on aggregated risk as estimated through studies such as genome-wide association studies. However, since most genome-wide association studies have been conducted in the non-Hispanic White populations, polygenic risk scores are not appropriate for use in the clinic.**
- **Common variants identified by genome-wide association studies each confer low risk.**

AD, albeit to a small degree. However, even after accounting for the aggregate load of common genetic risk in an individual, "missing heritability" still needs to be explained.[56] In other words, the common genetic variants do not account for the degree to which AD appears to be heritable. Furthermore, as sequencing became more accessible to both clinicians and researchers, it was clear that many families with multigenerational AD did not carry one of the known autosomal dominant genes. Next-generation technology facilitated sequencing the entire coding region (ie, exome) of genes, which paved the way for querying more directly the sequence variants in candidate genes as well as for broadly searching for coding sequence variants in families to detect variants that segregate with disease. Investigators were then able to detect rare variants (occurring at a frequency < 1%) that could explain some of the missing genetic contribution to AD.

TREM2

Triggering receptor expressed on myeloid cells-2 (*TREM2*), an innate immune receptor, was first linked to human neurodegenerative disease in 2002. Variants in the genes encoding TREM2 receptor and its ligand DAP12 were known to cause an autosomal recessive neurodegenerative disease, polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL), also known as Nasu-Hakola disease.[57] In 2013, two studies were published describing the discovery of rare *TREM2* variants that conferred a higher risk of AD[58,59]; in the case of the *TREM2* R47H variant, an elevated risk is reported as an odds ratio of 1.73 to 2.49.[55] Until that point, all risk allele effects were dwarfed by the *APOE* ε4 allele; therefore, this finding was a significant step in understanding AD pathogenesis and heterogeneity. In fact, decades earlier, a patient with PLOSL was found to have cognitive impairment, amyloid plaques, and neurofibrillary tangles, leading the authors at the time to suggest a possible pathogenic connection between this gene and AD.[60] Because the TREM2 protein is only expressed on myeloid, or immune cells, the association with AD suggested that dysfunction of the innate immune system itself could independently drive initiation or progression of AD. Besides the R47H variant, the R62H variant has also been associated with AD in multiple cohorts, whereas additional nominated risk alleles remain to be replicated.[61] *TREM2* variants were later found to be associated with increased risk in an African American cohort,[62] although interestingly, the variants identified differed from those reported in the largely non-Hispanic White cohort of the original 2013 studies. The clinical features among individuals with *TREM2*-variant AD in the original studies were reported to be similar to those of typical late-onset AD, although age of onset was earlier, on average, by approximately 3 years.[58] A later study that investigated five families with *TREM2* R47H AD showed no impact of the variant on age of onset, but the variant did shorten disease duration. The study also found an additive effect of *APOE* ε4, which likely contributed to both risk and age at onset.[32]

SORL1

In 2007, investigators searched for candidate genetic variants in the endocytic pathway that had already been implicated in AD pathophysiology through neuropathologic and biochemical studies of brain tissue from patients with AD.[63] The protein product of *SORL1*, SorLA (also known as LR11), had been identified a few years earlier as an APOE receptor and found to be decreased in the brains of patients with Alzheimer disease.[64,65] The investigators found that common

variants in *SORL1* were linked to AD, a finding that has been replicated in later genome-wide association studies.[66,67] With the availability of next-generation sequencing, screening of many genes simultaneously (exome sequencing) allowed for gene discovery at a more rapid pace. Now families who had tested negative for the known autosomal dominant genes could be evaluated for new causative genes. These studies identified that rare coding (protein-changing) variants (<1% frequency in the population) in *SORL1* significantly increased the risk of AD in carriers.[68-70] The measured risk is likely related to the molecular consequence of the variant; premature termination coding variants have the highest risk effect compared to other protein-altering variants (ie, missense variants[71]), which are also found in the general population, underscoring that *SORL1* variants have decreased penetrance. *SORL1* is associated with both early-onset and late-onset AD. Clinically patients with *SORL1* variants are indistinguishable from patients with sporadic or genetically undefined AD. *SORL1* is a key endosomal/lysosomal pathway gene, which, among its many cargos, transports APP away from the endosome, where it would be cleaved to form Aβ.[72] Therefore, impaired *SORL1* function due to genetic variation is predicted to alter Aβ processing and transport of cargo, which may contribute to cell dysfunction.[73]

KEY POINTS

- Rare variants confer risk in a range between common variants and autosomal dominant AD.
- Variants in the *TREM2* gene are a risk factor for AD.
- Variants in *SORL1* are found in sporadic and familial AD.

ABCA7

ATP binding cassette subfamily A member 7 (*ABCA7*) was first associated with AD risk in 2011 through genome-wide association studies because it was one of several genes within the genomic risk region linked to AD.[74] By design, genome-wide association studies identify common risk variants that generally have low odds ratios, or risk of developing disease. However, within a few years, investigators had leveraged existing genomic data to test for associations between ABCA7 protein-changing variants and found that rare loss of function missense variants were associated with an odds ratio of 2.03 in a population from Europe and the United States.[75] A focused *ABCA7* sequencing study in a Belgian cohort demonstrated an enrichment of loss-of-function *ABCA7* variants in individuals with AD, resulting in a relative risk of approximately 4.[76] Studies within the African American population have also identified missense variants conferring higher AD risk, for example, *ABCA7* p.Asn718Thr, which was associated with an odds ratio of approximately 4.[77] How *ABCA7* contributes to AD pathogenesis is not yet clear but may relate to impaired lipid metabolism.[78]

PLCG2 and *ABI3*

A large genome-wide association study of participant samples from the International Genomics of Alzheimer's Project replicated the earlier rare *TREM2* variant findings but also revealed novel rare variants in two genes implicated in the immune response, *PLCG2* and *ABI3*.[79] Interestingly, in contrast to other variants, the rare *PLCG2* R552R allele conferred protection rather than increased risk in AD, whereas the *ABI3* variant increased risk of AD with an odds ratio of 1.4. The *PLCG2* and *ABI3* risk variant findings have been replicated across ancestries, including European American, European, Argentinian, and African American cohorts.[80-84]

Other Rare Variants

Ongoing sequencing efforts, including genome-wide exome and genome sequencing, continue to discover or replicate rare gene changes that influence

AD risk or age of onset by a measurable factor.[84-86] Rare variants in *BIN1* and *ABCA7* were identified when investigators took a closer look at the coding region of these genes after genome-wide association studies had nominated them as candidate genes of interest.[87-89] Other rare variants, such as those in *UNC5C*, were detected through sequencing studies of families with autosomal dominant AD.[90] Variants in *AKAP9* were first identified in familial African American cases, and the association was replicated in a larger African American cohort.[88,91-93] In some cases, conclusions have differed regarding rare variants, as in the *CLU* gene, which was also first identified in genome-wide association studies as a candidate gene.[50,52,94] Additional rare variants in genes *INPP5D, NME8, CR1, EPHA1,* and *CD33* have all been identified in both genome-wide association studies and rare variant studies.[91] All of these findings add to the understanding of vulnerable cell populations and the pathogenic mechanisms that drive AD. The diversity of cellular functions implicated by the growing list of rare and ultrarare variants associated with AD underscores the pathogenic heterogeneity, highlighting the many opportunities for meaningful disease intervention.

PROTECTIVE FACTORS

With genome-wide testing across large cohorts, genetic factors that may protect from AD can now be sought. By leveraging genetic data from the more homogenous Icelandic population, investigators have recently discovered a missense *APP* A673T variant that is protective against AD and leads to decreased Aβ production in vitro.[16] These findings strengthen the link between Aβ and AD risk, although the exact mechanisms through which the two are related remains unknown. A similar example of an AD-associated gene conferring both risk and protection is *ABCA7*. A relatively uncommon missense variant in *ABCA7* (allele frequency of approximately 4%) was found to confer protection in a cohort of sporadic AD and controls of British and North American ancestry.[95]

One of the well-studied genetic modifiers of the *APOE* ε4 allele is Klotho, a protein implicated in aging.[96] The Klotho "VS" variant confers relative protection from Aβ deposition and risk of AD in *APOE* ε4 carriers.[97,98] Although additional studies are needed to confirm the association, an *APOE* variant previously associated with hyperlipidemia,[99] the Christchurch mutation, was reported in an individual from a large Colombian kindred that carried the *PSEN1* E280A variant. Although these families typically have an average age of AD onset of 49 years, this individual did not develop AD symptoms until her seventies.[17] Because autosomal dominant familial AD shows a general association between variant and age of onset, studies of genetic modifiers of disease are higher powered in families or kindreds who carry the same pathogenic variant. An association study performed in the Colombian *PSEN1* kindred revealed a *CCL11* missense variant correlated with a 10-year delay in age at disease onset.[100] The *CCL11* protein product, eotaxin, has a chemokine-regulating immune function with a putative role in aging and is thus an example of pathways that may be shared between sporadic and monogenic AD that could be targets for disease-modifying therapies.

GENETIC TESTING

This article began with a question often asked by patients: What is my risk for disease? In autosomal dominant AD due to *PSEN1, PSEN2* and *APP*, technologic and commercial changes in sequencing in the past 10 years have made testing

more feasible in the clinic. As discussed above, however, families with mendelian forms are rare. Once high-throughput sequencing facilitated genetic testing in well-phenotyped research cohorts, it became apparent that even in patients with an age of onset younger than 65 years, the rate of carrying a pathogenic variant in an established AD gene is low, estimated at between 1% and 6%.[8,101,102] In the author's clinic, for individuals with a family history of early-onset AD and for those with an early onset (younger than age 55) even without a family history of AD, a discussion regarding genetic testing for *APP*, *PSEN1* and *PSEN2* is typically initiated if patients have not raised the question themselves. The clinical overlap between other dementing diseases, including frontotemporal dementia, genetic prion disease, and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), warrants considering genes associated with neurodegeneration other than AD. Next-generation sequencing technology has resulted in commercial genetic testing panels that are more cost effective than single-gene testing. Therefore, the author sends a dementia genetic panel for patients with early-onset AD-type dementia. In some cases, patients are interested in genetic testing because of a family history less suggestive of a mendelian AD, such as one or two relatives with late-onset AD. In those cases, the patient or family is counseled on the very low likelihood that the dementia is caused by a single gene change.

When individuals who are suspected of carrying an AD gene have tested negative on a focused panel of established dementia genes (such as the three AD genes as well as frontotemporal dementia–associated genes [*MAPT*, *GRN*, *TBK1*, *C9orf72*] and *PRNP*, which causes prion disease), little appears to be gained from proceeding to expansive exome sequencing.[101,102] Therefore, although exome sequencing has been pursued on a large-scale research basis, it remains of limited use in the clinic.

Genetic Counseling

Unlike other laboratory tests routinely sent for dementia, such as thyroid-stimulating hormone (TSH) or vitamin B_{12} level, genetic testing is complicated by the potential implications for employment, insurance coverage, and other family members. In neurodegenerative disease, genetic testing has one or more of the following purposes: diagnostic, predictive, or to inform prognosis.[103] When asymptomatic individuals know they are at risk for a mendelian disease and pursue genetic testing, it is considered predictive testing. Reasons to choose genetic testing include family planning, career and life planning, and often because individuals "just want to know" (in some cases, the anxiety of not knowing one's gene status can itself be overwhelming). If the neurologist is presented with a patient whose history and clinical features warrant genetic testing, it is strongly recommended to proceed with testing in consultation with a genetic counselor. Genetic counselors are specialized practitioners with graduate-level training in clinical, molecular, and biochemical genetics. Thus, their specialty bridges the patient's family history and clinical phenotype, with the knowledge of risk genes and interpretation of genetic variants.

Patients hope that testing will be negative, and many start the testing process with little else in mind. The clinician and genetic counselor should facilitate consideration of the ramifications of testing, whether results are negative or positive. Ideally, patients undergo a three-visit series similar to Huntington disease genetic testing protocols[104]: pretest counseling with the genetic

KEY POINTS

- Some gene variants may be protective against AD.
- Genetic testing should start with a dementia panel, although beyond a panel, yield is very low.
- Genetic counseling is strongly recommended for genetic testing, particularly in the at-risk asymptomatic individual.
- Genetic counselors are clinicians trained in molecular and clinical genetics. They provide education to patients deciding whether to pursue genetic testing in precounseling visits and counseling when disclosing results.

counselor, a discussion and examination by the physician with testing if indicated, and a results visit with both the genetic counselor and physician. At the initial pretest visit, the genetic counselor discusses the patient's motivation for testing and potential impacts to the patient's psychological well-being, work, social interactions, and other family members who will potentially learn genetic information indirectly. The genetic counselor may identify potential concerns to suggest that significant risk of adverse psychological impacts exists if testing is pursued at that time. After pretest genetic counseling, some individuals decide that testing is not right for them at that time and may reconsider testing later, as exemplified by the patient's brother in CASE 10-1. The consequences of receiving a positive gene test result for an asymptomatic individual can be powerful. Individuals may feel shocked, depressed, anxious, guilty, or suicidal. Past or present poorly managed depression or history of suicidal ideation may prompt a referral to counseling or psychiatry before initiating testing. However, news of a positive result can also make patients feel more informed or inspired. In some cases, psychological pressures arise from delaying testing, in which case the clinician and genetic counselor identify a management team that includes a mental health counselor to support the patient through the testing process and after results are received. A negative gene test in someone with other affected family members, particularly siblings, can sometimes lead to "survivor guilt," a phenomenon again expertly addressed by genetic counselors.

Individuals who are not prepared to receive genetic testing but would like to have that choice available to relatives after their death may choose to bank DNA to be accessible for testing by family members. For patients near institutions with neurogenetic counseling, a referral can be made; however, many patients live in regions without immediate genetic counseling support in their clinics. Physicians may contact the closest academic center to identify recommended genetic counseling services in the state, many of which now offer telemedicine counseling.

Diagnostic genetic testing for patients who are symptomatic is typically performed in concert with a family member or guardian as informed consent may not be feasible in patients with dementia. Because the results of testing will have implications for the family and potentially for prognosis, genetic counseling remains indicated. Ideally, surrogate decision makers consider whether testing is consistent with the patient's wishes based upon available information and avoid any adverse implications to the patient when making testing decisions. The cost of genetic testing is variable, ranging from hundreds to thousands of dollars for a gene panel. Insurance does not routinely cover neurodegeneration gene panels. Therefore, before any testing, counselors and physicians should make patients aware of the potential out-of-pocket costs. Because genetic testing does not necessarily change medical management significantly, some individuals in the author's clinic choose not to test given the cost and instead bank DNA for future testing, if indicated.

A number of opportunities to engage in research through clinical trials are available for individuals with genetic forms of AD or who have a family history of monogenic AD. For example, the Dominantly Inherited Alzheimer Network (DIAN) and the Alzheimer's Prevention Initiative conduct longitudinal and interventional studies for individuals who have or are at risk for autosomal dominant AD.

For those who have tested positive or do not wish to know their genetic status, preimplantation genetic diagnosis is an option when family planning. Again, genetic counselors and clinics are a valuable resource for directing interested

individuals for this and other reproductive planning options. Since the passing of the US Genetic Information Nondiscrimination Act (GINA) of 2008, genetic test results cannot be used by insurers to deny health insurance in the United States. This protection does not extend to long-term care insurance, life insurance, or disability insurance. Many individuals in the author's clinic who proceed with predictive testing will establish these additional insurance policies before testing. Title II of GINA protects individuals from employment discrimination, which is defined as hiring decisions, firing, promotions, pay, and job assignments, based on genetic information. Although it is encouraging that genetic status is covered by some degree of protection, it is important to note that GINA is statutory law and is not guaranteed to remain as it is currently defined.

APOE Testing

Despite the extensive use of *APOE* genotyping in research and clinical trial settings, because *APOE* ε4 is neither sufficient nor necessary for the development of AD, it is not a clinically useful predictive test.[106,107] Nevertheless, genetics has risen to the forefront in popular culture and has piqued patients' interest regarding how genetics relates to their own health. Direct-to-consumer testing plays an evolving role in research, self-directed patient care, and genetic counseling. *APOE* alleles are being reported through direct-to-consumer testing companies, and patients are now able to obtain their own genotype information, although typically without the benefit of the face-to-face genetic counseling available in a clinic. At the time of this writing, the author's clinic routinely receives self-referrals from individuals with normal cognition who have pursued direct-to-consumer testing, learned of their *APOE* status, and request a genetics evaluation to understand the implications of results. Previous work by the REVEAL (Risk Evaluation and Education for Alzheimer's Disease) study established that individuals received information about their *APOE* status quite well and without untoward effects, although importantly, these results disclosures were performed in a controlled setting with a multidisciplinary team that included clinicians and genetic counselors.[108]

THE FUTURE OF ALZHEIMER DISEASE GENETICS

The risk of dementia varies across ethnicities.[109] Thus, since most of the genome-wide association studies have been in the non-Hispanic White population, the generalizability is limited and constrains the ability to provide more tailored and presumably more effective therapies. An AD genetic study described an *ABCA7* deletion that increases risk for AD that is common in the African American population but low in the non-Hispanic White population, demonstrating how underlying differences in population risk can include the relative frequency of an allele in the population.[110] It is well established that the frequency of SNPs varies across populations; therefore, distilling risk from genome-wide association studies has limited applicability.[111] Nearly 80% of all genome-wide association studies are conducted in individuals of European descent, and thus polygenic risk scores based upon genome-wide association studies are accurate specifically for those populations.[112] This tremendous disparity in AD research is now considered a priority by the National Institutes of Health. It is hoped that increased recruitment of diverse populations and funding of diversity-incorporating genetic studies will help us reach parity in AD clinical research and grow closer to health care equity.

KEY POINTS

- **Individuals who do not want to undergo genetic testing immediately but want to have that option available to family members after their death may consider DNA banking for future testing.**
- ***APOE* genotyping is useful in clinical trials and research, although it has limited utility in the clinic.**
- **Our understanding of AD will be massively strengthened as the cohorts being studied are broadened, moving us closer to tailored AD therapies.**

CASE 10-1

A 37-year-old man was referred to the clinic for cognitive symptoms and "jerking." His father, who accompanied him, reported that 5 years earlier the patient began to experience mild behavioral changes, including increased anxiety. Three years before this evaluation, the patient began to report that he was having difficulty at his work in a store warehouse, with difficulty remembering tasks and completing complex activities that he had been doing for years. He left his job because of disability and within 1 year was living with his father. At the time of evaluation, the patient was unable to prepare meals, drive, or pay bills. He spent his time watching television or playing simple video games. He had no other medical conditions.

The father provided the history that he had separated from the patient's mother and had no further interaction with her, although he had been told the mother had developed early-onset dementia in her thirties or forties. The patient's maternal uncle had also been diagnosed with memory problems in his late thirties. The maternal grandfather had died in his forties, again with memory problems.

On examination, the patient had occasional myoclonic jerks in both arms. He was oriented to season and that he was in a clinic setting but was otherwise inaccurate with orientation questions. He could not perform simple subtraction or addition and had 0/3 recall. He showed no cerebellar signs and had normal tone and reflexes and normal gait.

A brain MRI was performed, which demonstrated moderate cerebral volume loss in the bilateral parietal and anterior inferior temporal lobes (FIGURE 10-1).

Because of the strong family history of early-onset memory-predominant dementia and the lack of a history of prominent behavioral or language challenges, genetic testing for familial Alzheimer disease was pursued. A pathogenic variant that had been previously reported in *PSEN1* (the *PSEN1* M147L allele) was detected in the patient, which has been associated with typical Alzheimer disease and an average age of onset in the late thirties to midforties.[105] He died 2 years after diagnosis.

The patient's brother, 3 years his junior, had accompanied the patient and father to the genetic testing results visit. He was made aware of the implications the testing had for him and for his three children. Shortly after the patient's death, the brother presented to the clinic for genetic counseling. He did not have any subjective cognitive concerns or any evidence of cognitive impairment. After discussion with the genetic counselor regarding the potential benefits and risk of testing, he opted to defer testing for the time being. The stated reasons included that learning of a positive gene test would not cause him to change his medical care, lifestyle, or life planning. Additionally, his family continued to hold out hope that he had not inherited the disease gene, and testing could potentially remove that hope. He continued to remain connected with the physician and clinic knowing that he might eventually change his mind to test even if he remained asymptomatic.

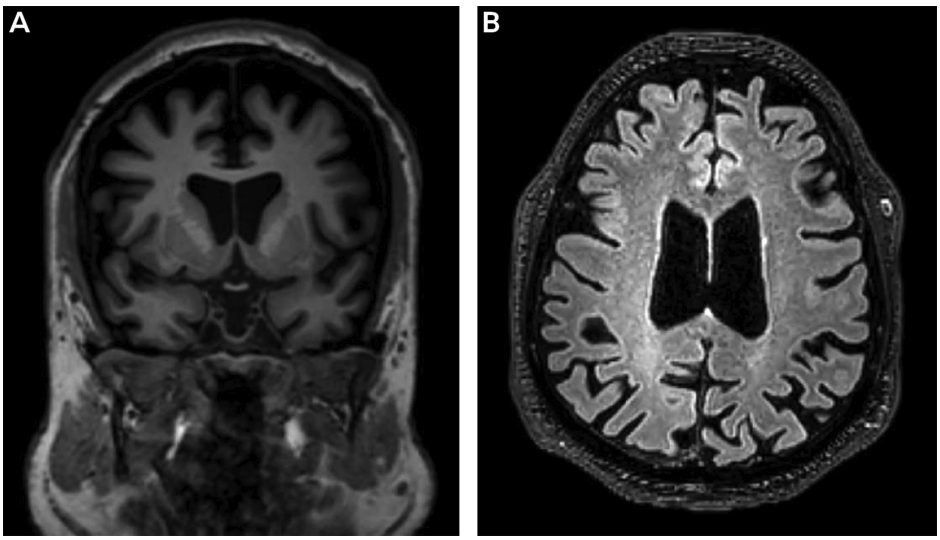

FIGURE 10-1
Imaging of the patient in CASE 10-1. Coronal noncontrast T1-weighted (*A*) and axial fluid-attenuated inversion recovery (FLAIR) (*B*) images show diffuse cerebral volume loss and marked bilateral parietal atrophy.

COMMENT

This case demonstrates the complexity of genetic testing in the clinical setting and the variability in individuals' perspectives on whether to pursue testing.

CONCLUSION

Our understanding of the genetic architecture of AD and the implications to diagnosis and therapy have evolved dramatically since the discovery of the *PSEN1*, *PSEN2*, and *APP* genes 30 years ago. With the collaboration of investigators and patient advocates, connections between the rare families with autosomal dominant AD have developed across the globe. Interventional trials for these families are under way for asymptomatic or early symptomatic individuals and will be available soon for those who are years away from their predicted age of onset.[113] Because drug trials can begin decades before clinical presentation in those known to carry autosomal dominant disease gene variants, the hope is that intervention may be early enough to be effective.

It is undeniable that, to date, results of clinical trials in AD have been disappointing. A path of drug discovery had begun, leveraging the knowledge that dysfunction of the biological processes, including those associated with amyloid, contribute to AD. Yet, despite the promise that there was a parsimonious explanation for the cause of AD suggested by the relationship of autosomal dominant AD genes and neuropathologic amyloid plaque, the path to translate that information to effective therapeutics has not yet been found. The genetic contribution to AD likely lies within various points along pathogenesis from the inciting event, such as amyloid or tau, to the cellular responses that may be protective or maladaptive and harmful. These biological processes follow a temporal relationship to biomarker and clinical changes. The ongoing genetic characterization of all forms of AD has provided a more textured understanding of AD pathophysiology and the multicellular environment in which AD-related neural changes develop. Numerous physiologic pathways from integrated genetic and human tissue molecular profiling have been identified, resulting in a menu of targets that can be screened on high-throughput platforms and human neural cell in vitro models, bioinformatically tested for druggability (potential for effective engagement and modulation by therapeutics), and evaluated for drug repurposing opportunities. All of these new avenues enrich the chances to find effective therapies.

The patient's intersection with genetics now has many more points, some of which occur outside the clinic. Patients can now submit their biological samples to sequencing companies and receive genetic information directly. As physicians, our role is to provide consultation while respecting autonomy. This balance may be tested to some degree, but with increased awareness in the general public and neurologists that the interpretation of genetic testing is complex and that patients can always benefit from genetic counseling, it is expected that the relationship of genetic counseling, neurologists, and patients will also continue to evolve with the times.

USEFUL WEBSITES

DOMINANTLY INHERITED ALZHEIMER NETWORK
This website provides information about an observational study and clinical trials for individuals and families with autosomal dominant Alzheimer disease as well as resources for families on genetic counseling and webinars.

dian.wustl.edu

ALZHEIMER'S PREVENTION INITIATIVE
This website provides information on prevention trials and biomarker studies as well as a patient registry.

banneralz.org/research-and-clinical-trials/api

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