New Genes and New Insights from Old Genes: Update on Alzheimer Disease

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ABSTRACT

Purpose of Review: This article discusses the current status of knowledge regarding the genetic basis of Alzheimer disease (AD) with a focus on clinically relevant aspects.
Recent Findings: The genetic architecture of AD is complex, as it includes multiple susceptibility genes and likely nongenetic factors. Rare but highly penetrant autosomal dominant mutations explain a small minority of the cases but have allowed tremendous advances in understanding disease pathogenesis. The identification of a strong genetic risk factor, *APOE*, reshaped the field and introduced the notion of genetic risk for AD. More recently, large-scale genome-wide association studies are adding to the picture a number of common variants with very small effect sizes. Large-scale resequencing studies are expected to identify additional risk factors, including rare susceptibility variants and structural variation.
Summary: Genetic assessment is currently of limited utility in clinical practice because of the low frequency (Mendelian mutations) or small effect size (common risk factors) of the currently known susceptibility genes. However, genetic studies are identifying with confidence a number of novel risk genes, and this will further our understanding of disease biology and possibly the identification of therapeutic targets.

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INTRODUCTION

The clinical and pathologic entity known as Alzheimer disease (AD)[1] is the most common cause of dementia, a problem that, considering increasing longevity, is growing in its public health implications.[2] Late-onset AD, the most common form of the illness (typically defined as onset after 65 years of age), is rarely caused by mutations transmitted in Mendelian fashion, and yet its heritability—broadly defined as the proportion of disease vulnerability due to heritable genetic factors—has been estimated to be somewhere between 58% and 79%.[3] Therefore, although cases of AD inherited in a Mendelian fashion are rare (accounting for approximately 1% of cases), genetic factors are likely to play an important role in all forms of the disease. Over the last 20 years tremendous advances have been made in genetic and information technology, such that novel approaches (including genome-wide association studies and whole-genome sequencing) have joined more traditional mapping methods, such as familial genetic linkage studies and candidate gene case-control studies, as powerful means to identify genetic variants associated with common diseases such as late-onset AD. Studying large populations with these sensitive techniques has

allowed the identification of several new genes consistently associated with AD risk. However, the overall magnitude of the risk conferred by each of these is small, and therefore the clinical relevance of these findings is as yet undefined. Nonetheless, study of the pathways through which these genes contribute to AD pathology is an avenue toward the identification of potential therapeutic targets. Because significant progress in developing treatments for AD has been lacking, such new approaches are of critical importance.

This review will discuss progress in understanding of the genetic underpinnings of AD, clinical relevance where applicable, and how this knowledge is guiding future research into treatments for and prevention of AD.

FAMILIAL ALZHEIMER DISEASE: MENDELIAN FORMS

The observation of the familial occurrence of AD dates back almost to Alois Alzheimer's initial description of the disease, before dementia of late onset was understood to have a similar underlying pathology. However, the genes underlying these rare forms of the illness remained elusive until the early 1990s, when cloning and linkage studies allowed for the identification of three genes that cause this fully penetrant, early-onset, autosomal dominant form of the disease: amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2). Mutations in the APP gene were identified first,[4] 4 years after the amyloid precursor protein was discovered to be the major component of senile plaques[5] and cerebral blood vessel amyloid[6] and mapped to chromosome 21.[7–9] In 1995, young-onset familial AD was linked to chromosome 14 in some families, and subsequently the PSEN1 gene was cloned.[10] Around the same time, linkage was made in the Volga-German AD kindred to a gene on chromosome 1 that was highly homologous to PSEN1 and was ultimately dubbed PSEN2. It was subsequently recognized that the pathogenic alterations of these genes all contribute to the increased absolute or relative production of the 42-amino-acid–length cleavage product of APP[11] (the Aβ42 version of the amyloid-β [Aβ] peptide), which is a major constituent of the plaques that characterize the illness. Further in vivo and in vitro work served to support this "amyloid cascade hypothesis" of AD etiology (recently reviewed by Benilova and colleagues).[12] Simply put, it is speculated that increased production or decreased elimination of the Aβ peptide is the trigger initiating a series of events ultimately leading to the pathology and clinical manifestations of the various forms of AD. Further genetic evidence supporting this hypothesis is that subjects with Down syndrome (who have three copies of chromosome 21),[13] mosaicism for trisomy 21,[14] or duplications of the APP gene[15] can all develop AD pathology. Although this predominant hypothesis has led to important insights into the pathologic cascade leading to AD, this knowledge has yet to translate into meaningful interventions. Indeed, it may be possible to clear the deposited fibrillar forms of Aβ without significantly influencing clinical disease.[16]

Although substantive disease-modifying interventions do not yet exist, these advances have enabled definitive diagnosis of familial AD and therefore can have significant effects on patients and their families in terms of understanding the illness, its inheritance, and its prognosis. Furthermore, this progress allows for the possibility of presymptomatic testing in unaffected at-risk subjects. Therefore, clinicians should

have a thorough understanding of the phenotypes and of testing that is available.

Amyloid Precursor Protein

Mutations in the *APP* gene encoding for amyloid precursor protein were the first mutations identified to cause familial AD and are currently the second most common cause of familial AD. Twenty-four mutations have been reported that are thought be pathogenic (*www.molgen.ua.ac.be/ ADMutations*), are concentrated near the N-terminal (the β-secretase cleavage site) and C-terminal (the γ-secretase cleavage site) ends of the Aβ portion of *APP*, and affect the amount of Aβ produced by cells. The V717I substitution in *APP*, occurring near the γ-secretase site, was the first described familial AD mutation[4] and appears to have arisen independently in white, Japanese,[17] and Mexican[18] populations. In addition, several *APP* variants associated with familial AD have been described that occur within the Aβ sequence. In vitro studies of some of these mutations indicate that the mutant protein resulting from such alterations self-assembles more efficiently, which is hypothesized to ultimately result in more rapid aggregation in the brain. The nature of the amyloid pathology can differ in people with these mutations, such that plaque morphology can be distinctive[19] with excessive deposition.[20] Such pathology sometimes results in cerebral infarcts or hemorrhages that can be a major aspect of the clinical presentation.[20,21] More recently, duplications of the *APP* locus have also been identified in familial AD associated with cerebral amyloid angiopathy (CAA),[15] confirming that these mutations cause familial AD through a ''gene dose'' effect in increasing Aβ production. Further support for the amyloid hypothesis comes

from the recent discovery of a variant near the β-secretase cleavage site (A673T) in *APP* that is associated with decreased production of Aβ and a decreased risk for late-onset AD.[22] This supports the assertion that pharmacologic inhibition of β-secretase activity is a promising direction to pursue in developing therapies to treat or prevent AD.

Presenilin 1

PSEN1 mutations are the most common cause of familial AD; 197 variants have been preliminarily associated with familial AD (*www.molgen.ua.ac.be/ ADMutations*). Of these, a few lack confirmation, or there are reasons to suspect pathogenicity, such that 185 are currently thought confidently to cause familial AD. The majority of these are missense mutations causing amino acid substitutions in the coding region of the gene, although a few consist of insertions or deletions of portions of the protein. The Presenilin 1 protein (PS1) was identified to be the catalytic site of the γ-secretase complex that cleaves the APP protein to produce Aβ fragments.[23] By causing conformational changes in PS1,[24] the majority of pathogenic *PSEN1* mutations cause an increased absolute or relative production of Aβ42,[25] and it is thought that this is the mechanism through which they cause AD.

Although many of the 185 *PSEN1* mutations are described in single families, a few have been reported repeatedly and appear to represent founder effects. The E280A substitution, found in subjects from Colombia, represents the largest group of families and has been well characterized by investigators there.[26] The G206A substitution was described in Caribbean Hispanics, mostly originating from Puerto Rico.[27] Another mutation (A431E) that has been repeatedly identified in people

whose family roots originate in the state of Jalisco in Mexico also appears to represent a founder effect.[28] The existence of these groups of familial-AD families of specific ethnic and geographic origins indicates that inquiring about patients' ancestral origins can be informative.

PSEN1 mutations tend to cause the youngest age of symptom onset (44–46 years of age in one series).[29] However, unusual rare cases of onset as young as the twenties[30] and a family with a mean age of onset as late as age 76 (bearing the A79V substitution) have been described.[31] PSEN1 mutation carriers are more likely to have the atypical features that sometimes accompany familial AD, including spastic paraparesis,[32] early myoclonus, and seizures.[33] In a retrospective chart review comparing clinical features between 32 patients with familial AD due to PSEN1 mutations and 81 patients with nonfamilial early-onset AD, those with PSEN1 mutations tended to be younger (42 versus 56 years of age at onset), more likely to have memory complaints as the presenting feature (84% versus 58%, with nonfamilial cases frequently presenting with visuospatial and language deficits), and more likely to experience significant headaches, myoclonus, gait abnormalities, and pseudobulbar affect.[34] The presence of such features in a young-onset case of AD when the family history is unavailable should prompt the clinician to consider genetic testing.

Presenilin 2

Mutations in the PSEN2 gene are rarest and tend to have the oldest and most variable age of onset.[29] Of 21 variants in PSEN2 described on www.molgen.ua.ac.be/ADMutations, possibly only eight,[35] or at most 13, are thought to be pathogenic for AD. This includes a large Volga-German

founder effect mutation (N141I). People with PSEN2 mutations have a mean age of onset of 54 years, with a range from 39 to 75 years of age in one series.[35] Among people with the N141I mutation, seizures were present in 31%. Because the pathogenicity of identified variants in PSEN2 is not always clear, caution needs to be exercised when interpreting results of such testing with patients and their families (Case 3-1).

Insights into Late-Onset Alzheimer Disease Derived from Familial Alzheimer Disease

As described above, the discovery that the pathogenic mutations in familial AD genes affect the catabolism of APP, causing the increased absolute or relative production of the amyloidogenic form of the Aβ peptide, fueled the amyloid cascade hypothesis of AD. Although increased production of these forms of Aβ has not been consistently demonstrated in late-onset AD, it is thought that a decreased ability to eliminate Aβ may lead to its oligomerization, toxicity, and ultimately cerebral deposition in this more common form of the disease.

Unlike late-onset AD, in which the ability to predict the future development of disease is imperfect, the study of asymptomatic people carrying familial AD mutations, who are essentially certain to develop the illness, allows biochemical, imaging, behavioral, and cognitive changes occurring very early in the disease course to be identified.[37] Many reports of relatively small series of such subjects have provided important insights, with studies of the Colombian kindred carrying the E280A PSEN1 mutation being the largest. Studies of this population have documented the course of cognitive decline[38] and, more recently, have provided insight into the course

Case 3-1

A cognitively intact 38-year-old woman presented with concerns that she was going to develop familial Alzheimer disease (AD) because a genetic test had come back positive for a *PSEN2* mutation. Further inquiry into the patient's family history revealed that her father had developed AD symptoms in his mid-sixties and died of the disease at age 74; his mother and father were not known to have had dementia, although one of his three siblings had dementia thought to represent AD, with onset of symptoms in his early seventies. The patient's mother was still alive and well at age 71.

Review of the commercial test results showed a S130L substitution in *PSEN2* that had been previously reported to be associated with AD. However, review of the reported cases showed an association in individual patients, including some with late onset, and segregation with the disease within a family had not been demonstrated. In addition, in vitro studies of this variant indicated it did not increase the amount of amyloid-β 42 (Aβ42) or the ratio of Aβ42 to Aβ40 produced.[36] On the AD and frontotemporal dementia (FTD) mutation database website (*www.molgen.ua.ac.be/ADMutations*), it was listed as "pathogenicity unclear." This information was conveyed to the patient, who was relieved to find out she was unlikely to develop AD of young onset.

Comment. This case illustrates many points. First, when autosomal dominant AD of young onset is suspected, it is preferable to perform genetic testing on a related affected person to know whether there is something that can be tested for before performing presymptomatic testing. In this case it may well have revealed that her affected father did not carry this variant. Also, not all reported variants are pathogenic, and it can take some knowledge of the field and research to interpret the results of a given test. The history in this family does not make a strong case for young-onset autosomal dominant disease. Finally, presymptomatic patients should always undergo genetic counseling before testing, in part to prepare them for the possibility of an inconclusive result.

of biomarker changes.[39,40] In addition, a separate international consortium of sites has been established to increase the number of people at risk for familial AD mutations that might be studied (the Dominantly Inherited Alzheimer Network, or DIAN, NIH U01 AG016570). Collectively, these efforts have confirmed that these mutations lead to increased levels of Aβ42 measurable in plasma and CSF. They have also suggested a sequence of biomarker changes in which decrement of Aβ42 in the CSF, cerebral deposition of fibrillar amyloid detectable with nuclear imaging, increased levels of tau in the CSF, decreased cerebral metabolism in certain brain areas, and cerebral atrophy on MRI occur in a fairly predictable manner.[41] This knowledge increases our understanding of the disease process and establishes the characteristics of biomarkers that can be used as surrogate outcome measures in prevention trials. Indeed, with the recent failure of promising antiamyloid approaches to treat late-onset AD in large Phase III trials, there is increasing attention toward prevention of the disease. Trials to prevent familial AD by administering experimental medications to asymptomatic mutation carriers are in development and should commence in 2013.

APOLIPOPROTEIN E

ApoE is a protein involved in lipid transport that acts as a scaffold in high-density lipoprotein (HDL) particles and is highly expressed in the liver and in the CNS, where it is made by astrocytes and microglia. In addition to transporting lipids, it also has a role in the transportation of forms of Aβ including Aβ42. In humans, the gene for ApoE (*APOE*) is highly polymorphic; the *APOE*E3* allele is the most common, followed by the *E4* allele, which is in turn more common than the *E2* allele. The *E3*, *E4*, and *E2* alleles, which differ in only one or two amino acids, have been reproducibly shown to have differential effects on risk of late-onset AD, with *E4* conferring a greater risk than *E3*, which in turn confers a higher risk than the *E2* allele, with odds ratios between approximately 4 for heterozygous and approximately 15 for homozygous carriers of the *E4* allele.[42]

Multiple mechanisms through which the different ApoE forms may mediate the differential risk for AD have been identified (reviewed by Kim and colleagues[43] and Verghese and colleagues[44]), including differential effects on Aβ transport and deposition. Human pathologic studies show a positive correlation between *E4* allele dose and amyloid[45] and neuritic plaque density[46] at autopsy. Studies in cognitively normal individuals have demonstrated that carriers of the *APOE*E4* allele have higher amyloid binding on imaging and lower Aβ42 levels in CSF (suggestive of its deposition in the brain) than do noncarriers.[47]

Work in transgenic mice has begun to elucidate the mechanistic role for ApoE in amyloid transport and deposition. Amyloid deposition in mice with human APP mutations was diminished when crossed with ApoE "knockout" mice.[48] Furthermore, the amount of Aβ accumulation differed in mice transgenic for human ApoE in an isoform-specific way, such that it was greater in *E4* mice than in *E3*, where it was in turn greater than in *E2* mice. In vitro studies suggest that ApoE, particularly the *E4* form, promotes fibrillogenesis of Aβ.[49] Lipidation of particles containing ApoE may be required for amyloid clearance, as mice devoid of the ATP binding cassette 1 (ABCA1), which lipidates ApoE, show increased amyloid deposition,[50] and overexpression of ABCA1 reduces amyloid deposition.[51] Microdialysis experiments in transgenic mice suggest that ApoE isoforms differentially influence Aβ clearance such that *E4* clears Aβ more slowly than does *E3* or *E2*.[52] There is therefore ample convergent evidence for ApoE as a potential therapeutic target for disease-modifying interventions in AD. Multiple ways of influencing the Aβ clearance through the ApoE pathway have been suggested, including ApoE mimetics[53] and stimulation of its production with peroxisome proliferator-activated receptor-gamma (PPARγ) agonists[54] and the liver X receptor (LXR) agonist bexarotene.[55]

The prevalence of the *E4* allele in the population varies depending on ethnicity but is typically in the range of 15% to 20%. Among people with AD, the prevalence is around 50%, again depending on the specific population being studied. The increased risk conferred by the *E4* allele is generally thought to be a three- to fourfold increase, and the lifetime risk of developing AD in someone with this polymorphism is 50% among those who live to be 80 years of age. Having two copies of *APOE*E4* increases the risk of a younger age of AD onset and makes the development of AD by age 80 highly probable.[56] It must be remembered, however, that most of these studies have been performed in

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white subjects; it appears that the risk for AD conferred by the *E4 allele in Latino populations is lower.[57] Although judicial use of *APOE* testing in young-onset cases can be informative (**Case 3-2**), presymptomatic susceptibility testing is not typically recommended (see guidelines below) because of the poor predictive value, variability in risk conferred across ethnic groups, and lack of definitive treatment options. However, in light of the increasing research interest in preventing AD and the possible differential response to future AD treatments depending on *APOE* genotype, investigators have begun to look at the effects of revealing the *APOE* genotype to asymptomatic patients in controlled settings, most notably in the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study. In this study, subjects potentially interested in knowing their genetic status are randomized to either receive this information or not, and various longitudinal assessments of their psychological reactions and understanding are made. This study has

so far found that, among the highly educated and engaged participants, the risk of adverse sequelae in the short term was not significantly increased,[58] but long-term retention of specific lifetime risk information was low. Studies such as this will help guide medicine as it becomes increasingly personalized, largely because of our increasing understanding of the genetic underpinnings of illness.

A recent study proposed that a repeat polymorphism within the neighboring *TOMM40* gene explains part of the risk traditionally attributed to the *APOE* locus.[59,60] Independent studies could not detect this effect after correcting for *APOE* genotype,[61,62] so this association remains controversial.

VARIATION IN FAMILIAL ALZHEIMER DISEASE GENES IN LATE-ONSET ALZHEIMER DISEASE

Late-onset AD also has a familial tendency that may or may not have an autosomal dominant pattern of inheritance. In such cases, competing mortality, in which people destined to

Case 3-2

The 40-year-old son of a 63-year-old man diagnosed with Alzheimer disease (AD) presented because of concern regarding his own risk for developing AD. His mother had AD at age 80, and his father's brother had it at age 70. Because of the patient's concern for developing the same problem, he had his father tested for *PSEN1, APP,* and *PSEN2* mutations by another doctor; all were negative. Despite this, he was still concerned that he would develop the same disease his father had and was seeking further help.

After discussing the implications of the various possible results, *APOE* testing was sent on the affected father by his treating physician, as a result of which he was found to be an *E4/*E4 homozygote. This provided an explanation for the relatively young onset of disease in the patient's father. Although the patient now knew he was at increased risk for developing AD, he was relieved to know that it was not autosomal dominantly inherited disease of young onset.

Comment. This case illustrates how judicial use of *APOE* testing can relieve anxiety but should be done only with oversight from a knowledgeable clinician rather than in a direct-to-consumer fashion. (See Guidelines for Genetic Testing in Alzheimer Disease).

develop AD die of other causes before manifesting the illness, can be one factor making the inheritance pattern difficult to interpret. In light of the continuity in phenotype between familial AD and late-onset AD, it is of interest if alterations in the genes for familial AD also contribute to the risk of late-onset AD. Unbiased genome-wide association studies typically fail to show a relationship between familial AD genes and risk of late-onset AD, including a recent study that looked at single-nucleotide polymorphisms (SNPs) from 3,940 cases and 13,373 controls.[63] A study was recently performed[31] in which the *APP*, *PSEN1*, and *PSEN2* genes were sequenced in patients affected by late-onset AD, and the frequency of variants compared between affected individuals from families in whom four or more members were affected and controls. Using this more sensitive approach, an increased frequency of variants in these genes was observed versus in controls and in reference databases. This included the A79V *PSEN1* mutation described above in which the age of onset is late, illustrating that continuity between familial AD and late-onset AD can occur.

OTHER RISK FACTORS FOR ALZHEIMER DISEASE
Common Variants

As with other complex diseases, families with familial AD and a Mendelian inheritance are a minority and explain only a small fraction of the estimated overall heritability. Although hundreds of genes have been implicated or studied at some point over the past 20 years in relationship with AD (for a catalog of candidate gene association studies, please refer to the AlzGene online database *www.alzgene.org*),[64] only recent, large-scale studies and rigorous statistical analyses (including

correction for population stratification) have allowed the identification of robust and replicable genetic risk factors for AD. Most of these susceptibility genes have been identified through large, collaborative genome-wide association studies, which consist of the assessment of hundreds of thousands of SNPs in a large number of cases and controls.[65] Most often, a replication series is studied to validate the results.

Four recent large collaborative genome-wide association studies and one meta-analysis identified or confirmed three novel genes or loci in 2009 (*CLU*, *CR1*, *PICALM*),[66,67] and six in 2011 (*ABCA7*, *MS4A6A/MS4A4E*, *EPHA1*, *CD33*, *CD2AP*, *BIN1*).[68–70] Clusterin (CLU), a ubiquitously expressed chaperone protein, is involved in transport, aggregation, and clearance of Aβ, and is present in Aβ deposits.[71] Complement receptor 1 (CR1) is a receptor for the complement C3b protein, an inflammatory marker of AD, and possibly protective against Aβ-induced neurotoxicity. Interestingly, the genetic susceptibility at this locus is probably linked to a copy-number polymorphism.[72] PICALM (phosphatidylinositol binding clathrin assembly protein) is a key component of clathrin-mediated endocytosis and is thought to be involved in Aβ clearance, possibly via endothelial cells.[73] Less is known about the more recently identified genes, but they have been linked to the same broad pathways of innate immunity (*CD33*, *EPHA1, MS4A*), Aβ production and clearance (*BIN1*), lipid metabolism (*ABCA7*), and intracellular transport (*CD2AP*).

A possibly unifying hypothesis for Mendelian rare variants and common risk genes could involve increased Aβ production in Mendelian forms of the disease, and impaired clearance (possibly caused by a myriad of genetic

KEY POINT
■ Although hundreds of genes have been implicated or studied at some point over the past 20 years in relationship with Alzheimer disease, only recent, large-scale studies and rigorous statistical analyses (including correction for population stratification) have allowed the identification of robust and replicable genetic risk factors for Alzheimer disease.

variants) in the late-onset, complex forms.[74] Population attributable fraction (the proportion of estimated genetic contribution explained) is approximately 28% for *APOE* and less than 10% for all other risk factors identified;[68,75] therefore, these 10 AD-associated variants (*APOE* and the additional nine named above) explain approximately 20% of the total variation of risk and approximately 33% of the risk attributable to genetic effects,[76] which suggests that numerous other factors of similar effect size wait to be identified.

Rare Variants

Whether the genetic contribution to AD and other common complex diseases comes from common or rare variants (or a combination) is a major issue in complex disease genetics.[77] Technical advances in sequencing now allow the sequencing of a large number of genes (or even the whole genome) in a large number of samples and will allow for the elucidation of the contribution of rare variation to the genetic architecture of complex disease.

Initial studies are beginning to identify and confirm the role of rare variation in AD susceptibility. A rare coding variant (A152T) in the gene encoding for the microtubule-associated protein tau (*MAPT*), in which other mutations cause FTD, has been associated with the risk of both AD and FTD in a study involving more than 15,000 subjects.[78] The above-mentioned rare variant in *APP* (A673T) has been identified in an Icelandic cohort and has a protective role.[22] Finally, two recent reports indicated that rare variants in the triggering receptor expressed on myeloid cells 2 (*TREM2*) gene increase the risk for AD.[79,80] TREM2 is an innate immune receptor expressed on the cell membrane of a subset of myeloid cells, including microglia. Although the sequence variants identified are rare, the identification of a novel gene will most likely generate new insights in the disease pathogenesis. Additional possible sources of susceptibility variants have not been studied extensively in AD. These include de novo variants, copy-number variation,[81] structural variation, and mosaicism.

Because of the small effect size (for common variants) and low frequency (for rare variants), the advances in genetics still have very limited clinical utility. Even in diseases in which hundreds of loci have been identified, such as inflammatory bowel disease, the predictive value for individual patients is still low.[82,83] The main, more attainable outcome of large-scale genetic studies is to identify loci related to disease susceptibility and thus gain insight into the biology of the disease, with the identification of genes and pathways involved in disease pathogenesis, and possibly novel therapeutic targets. The use of genetic assessment in clinical practice to guide treatment and predict outcome will probably be possible at some point in the future, but our current knowledge is still far from having an impact on clinical practice.

Guidelines for Genetic Testing in Alzheimer Disease

The most recent guidelines for genetic testing in AD were published in 2011 and represented a consensus from the National Society of Genetic Counselors and the American College of Medical Genetics.[84] Because the genetics of AD are complex, our current understanding is incomplete, and interventions proven to definitively prevent AD are lacking, genetic testing for AD should typically only be performed in consultation with a genetic counselor or other person versed in the genetics of AD.

Briefly, the guidelines can be summarized as follows: (1) a comprehensive family history should be obtained to reveal the likelihood, considering competing causes of death, of a family history of AD or other causes of dementia; (2) patients should be fully informed regarding the limits of the understanding of the genetics of AD and of the ability to treat or prevent it; (3) testing for AD in the pediatric population is not recommended; and (4) revealing testing for risk-susceptibility genes such as *APOE* is not widely recommended except in the context of fully informed patients and families, as in research studies. As such, direct-to-consumer *APOE* testing is not advised. With regard to testing for *APP*, *PSEN1*, or *PSEN2* mutations in symptomatic patients, (1) such testing should be offered in the context of a family history of autosomal dominant inheritance in which one or more cases are of early onset, or in young-onset cases with unknown family history (eg, adoption); (2) scientific literature and mutation databases such as the AD and FTD mutation database (*www.molgen.ua. ac.be/ADMutations*) should be consulted to help understand the likelihood of pathogenicity of a given mutation before revealing the result to patients and family members. Regarding the implications for asymptomatic people, (1) asymptomatic first-degree relatives should be informed of the 50% likelihood of inheriting the mutation and disease in the case of a pathogenic mutation being identified in an affected patient; (2) testing for asymptomatic at-risk subjects should be performed in accordance with the International Huntington Association and World Federation of Neurology Research Group on Huntington's Chorea Guidelines; and (3) people thought to be asymptomatic should undergo cognitive and psychological evaluations to better define their status and ability to comprehend and cope with results.

In the consensus statement from the National Society of Genetics Counselors and the American College of Medical Genetics, it was recognized that these guidelines were based on the current state of this rapidly changing field; that in any individual case, clinical judgment might supersede these recommendations; and that ethics committee consultation is recommended in challenging situations. The reader is referred to the full article for details.[84] With increasing understanding of the genetics of AD—and, hopefully, improvements in our ability to prevent and treat it—these guidelines will no doubt be subject to change.

SUMMARY

In the last 30 years there have been substantial advances in understanding of the genetic basis of AD, although genetic assessment is currently of limited utility in clinical practice because of the low frequency (Mendelian mutations) or small effect size (common risk factors) of the currently known susceptibility genes. However, genetic studies are identifying with confidence a number of novel risk genes that will improve understanding of disease biology and possibly the identification of therapeutic targets.

ACKNOWLEDGMENTS

KEY POINTS
- Ten Alzheimer disease–associated variants explain approximately 20% of the total variation of risk and approximately 33% of the risk attributable to genetic effects.

- Because of the small effect size (for common variants) and low frequency (for rare variants), the advances in genetics still have very limited clinical utility.

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