REVIEW ARTICLE
Key Words: Alzheimer's, genetics, comorbidity, epidemiology, apolipoprotein E

Genetics and Its Use in Alzheimer's Disease

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ABSTRACT *~ How useful is genetics to a clinician who treats patients with Alzheimer's disease (AD)? Even though much has been learned about the genetics of AD, given the current state of knowledge, the application of genetics to clinical practice is limited. Three genes (amyloid precursor protein [APP], presenilin 1, and presenilin 2) are primarily responsible for only part of early-onset AD, and the apolipoprotein E (APOE) gene elevates risk but does not confer risk deterministically. In addition, several candidate chromosomal regions are being investigated now. To accurately determine genetic profile so that it can be used in a clinical setting as a screening or diagnostic tool, much research is needed.* Psychopharmacology Bulletin. *2007;40(4):132–144.*

Introduction

AD is one of the most common neurodegenerative diseases, affecting over 15 million people worldwide. As populations age, in both developed and developing countries, the public health burden of AD will continue to increase. Since the early 1980s, tremendous progress has been made in our understanding of the genetics of AD; particularly, 4 genes have been identified and several candidate regions are currently being investigated. We have also identified several risk factors and comorbid conditions that increase the risk of AD. To devise effective prevention and treatment, however, we will need to better understand how these genetic and environmental factors contribute to AD. Here, we will discuss clinical and epidemiologic characteristics, environmental risk factors, and genes involved in AD with a focus on the role of APOE.

Clinical Characteristics

AD is the most frequent cause of dementia in adults. It begins with an impairment of memory. As the disease progresses, other intellectual skills become impaired and erratic behavior, delusions, and a loss of control over bodily functions occur. Language deteriorates gradually, with word-finding difficulty prominent in the early stages and

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impairment of verbal and written comprehension and expression in the later stages of illness. Spatial, analytic, and synthetic abilities and judgment are also affected with disease progression and may be accompanied by a loss of insight. Delusions and hallucinations are late manifestations and may include irritability, agitation, verbal or physical aggression, wandering, and a loss of emotional inhibition. Self-care and control over bodily functions become difficult in the final stages of the disease.

Criteria for the clinical diagnosis of AD were established in 1984.[1] Patients with no associated illnesses are termed *probable* AD, while *possible* AD includes patients meeting these criteria with other illnesses that could have caused central nervous system dysfunction, such as hypothyroidism or cerebrovascular disease. Although clinical diagnosis based on symptoms are quite accurate, the term *definite* AD is reserved for those patients in whom the disease has been confirmed at the postmortem examination.

PATHOLOGY AND FUNCTIONS

Microscopic neuropathological examination of the brain reveals deposits of extracellular β-amyloid (Aβ) protein in diffuse plaques and in plaques containing elements of degenerating neurons, termed neuritic plaques. Intracellular changes include deposits of abnormally hyperphosphorylated τ protein, a microtubule assembly protein, in the form of neurofibrillary tangles. There is also widespread loss of both neurons and synapses throughout. Additional features include other neuropil pathology (eg, neuropil threads), cellular pathology (eg, granulovacular degeneration in the hippocampus), and regional cell losses (particularly in the hippocampus). These degenerative changes occur first in a small region of the hippocampus before involving other brain structures.[2] The fundamental pathogenic mechanisms responsible for the development of these changes accompanying the disease are unknown.

These pathologic changes in the basal forebrain profoundly reduce its content of acetylcholine and the activities of cholineacetyltransferase and acetylcholinesterase. While other neurotransmitters can be involved, the loss of acetylcholine occurs early and correlates with the memory impairment. A variety of pharmacological interventions are available to improve the symptoms of the disorder. These medications include cholinesterase inhibitors, which increase central "cholinergic tone" and ameliorate secondary consequences of the disease.[3] However, there are presently no effective therapies proven to affect the course of this disorder.

DESCRIPTIVE EPIDEMIOLOGY OF ALZHEIMER'S DISEASE

The prevalence of AD before 65 years of age is <1%, but it increases dramatically (by 85 years of age and older, almost 30% of individuals

may have AD). In East Boston, Evans and colleagues[4,5] found that the prevalence of AD increased fifteenfold from 3% among individuals between 65 and 74 years of age to 47% for those individuals ≥85 years of age. Compared with some other studies, the prevalence observed in East Boston is higher because it included the full spectrum of disease from mild to severe forms.[6–12] However, similar rates have been found in the United States among African American and Hispanic populations.[9,13] Surprisingly, lower rates have been observed for Africans in the African continent.[14] It is worth noting that prevalence in different populations across different countries is difficult to compare not only for biological reasons but for a number of methodological reasons, including differences in culture, comparability of instruments, and diagnostic criteria.

The incidence rate for AD also increases with advancing age.[8,13,15–24] The average incidence rate increases from ~0.5% per year among individuals 65–70 years of age to ~6% to 8% for individuals >85 years of age. In some Asian and African populations the incidence rates are lower than estimates from more developed countries,[8,25] but in at least 2 studies individuals from African American and Hispanic ethnic groups appear to have higher rates of disease relative to white non-Hispanics.[13,23] These estimates should be interpreted with caution, since the exact age at onset and a disease-free population cannot be determined accurately.

Survival with AD varies from as short as 2 years to as long as 20 years. Two population-based studies found that the median survival is between 3 and 4 years.[26,27] AD increases the risk of mortality twofold,[26,28–30] particularly among men.

Medical and Environmental Risk Factors

Several medical disorders have been associated with AD. For example, AD occurs more frequently among individuals with a history of a prior depressive illness or a traumatic head injury than among those without these disorders.[31–36] Cardiovascular disease and dementia are frequent coincident disorders among the elderly. Heart disease and its antecedents, specifically hypertension, ischemic heart disease, hypercholesterolemia, and stroke, may predispose the elderly to AD.[37–41]

There are no specific environmental toxins known to be associated with AD. Cigarette smoking has been found to increase the risk of developing AD, particularly among those individuals without an APOE4 allele.[42–44] Socioeconomic factors may also contribute to disease risk because illiteracy, the lack of formal education, and even fewer years of formal education have been associated with AD.[45,46]

Several factors are reported to be protective against AD. The use of estrogen by postmenopausal women may result in a 50% reduction in

the occurrence of AD.[47–50] Anti-inflammatory agents also decrease the risk of AD.[51–53] Though not confirmed, wine in moderate amounts each day can reduce the risk of AD.[54] Time spent engaged in physical and mental activities during late life has been associated with a lower risk of AD.[55–57] Risk was lowest for those individuals with complex activity patterns that included frequent intellectual, passive, and physical activities. In the Canadian Study of Health and Aging, Laurin and colleagues[56] found that the strongest effects were related to physical activities such as vigorous exercise.

GENETIC EPIDEMIOLOGY OF ALZHEIMER'S DISEASE

A number of different studies clearly support genetic contributions toward AD. AD is more frequent among monozygotic compared with dizygotic twins, with heritability coefficients ranging from 0.28–0.58.[6,58] First-degree relatives of patients with AD, particularly siblings, have twice the expected lifetime risk of developing the disease.[59–61] Complex segregation analyses conducted on AD clinic patients and their first-degree relatives support the presence of major genes as well as contributions from other environmental risk factors.[62–64] As a confirmation of these studies, researchers have identified several putative genes from large multigenerational families with AD. Mutations in 3 genes, the APP gene on chromosome 21, presenilin 1 on chromosome 14, and presenilin 2 on chromosome 1, are usually found in families with an autosomal dominant pattern of disease inheritance beginning as early as the third decade of life (Table 1).[65] Over 100 mutations in presenilin 1 exist, making this the most common form of familial early-onset AD.[66] In a study of over 400 patients suspected of having early-onset familial AD and referred for genetic testing, 11% had mutations in presenilin 1. Studies of mutant genes from these families indicate that many lead to enhanced generation or aggregation of Aβ peptide that is subsequently deposited in the brain in the form of neuritic plaques, suggesting a pathogenic role.

One of the most important observations has been the identification of the relation between the APOE gene on chromosome 19 and AD (Table 1). It has been called a "susceptibility" gene because it does not cause AD deterministically, but rather it increases the risk of AD. Having 1 copy of the APOE-E4 allele is associated with a 2- to 3-fold increased risk, while having 2 copies is associated with a 5-fold increase. The population attributable risk associated with APOE4 may be as high as 30%, making it the single most important risk factor for the disease in elderly individuals. Each APOE4 allele lowers the age-at-onset by several years.[67] This common variant may influence the age-at-onset in some families with mutations in the APP gene[68] and in adults with Down syndrome who develop dementia as they age.[69]

TABLE 1

GENES AND OTHER CANDIDATE CHROMOSOMAL LOCATIONS ASSOCIATED WITH AD

CHROMOSOME	GENE	AGE AT ONSET (YEARS)	PATTERN*	VARIANTS/MUTATIONS
ch21q21.3	APP	30–60	AD	10 (exons 16, 17)
ch14q24.13	PS1	30–50	AD and familial	100 (exons 4–12)+
ch1q31.42	PS2	50–70	AD	6 (exons 4, 5, 7)
ch19q13.2	APOE	50–80+	Familial	3 isoforms
ch12p13†	?	>65	Familial	?
ch10q†	?	>65	Familial	?
ch9p†	?	>65	Familial	?

AD = Alzheimer's disease; APP = amyloid precursor protein gene; PS1 = presenilin 1 gene; PS2 = presenilin 2 gene; APOE = apolipoprotein E; ? = unknown.
*AD here refers to the Mendelian autosomal dominant pattern of inheritance.
†Chromosomal location identified by linkage.

Lee and Mayeux. *Psychopharmacology Bulletin*. Vol. 40. No. 4. 2007.

Genetic linkage studies show at least three additional putative loci with association to AD (Table 1). A locus on chromosome 12 conferring susceptibility was identified by Pericak-Vance and colleagues.[70] Subsequent confirmation been limited due to locus heterogeneity related to APOE4 and to clinical heterogeneity as a result of the identification of Lewy bodies in the brains of patients.[70–74] A locus on chromosome 10 has also been associated with AD and with a putative biomarker of altered Aβ in the plasma of family members.[75,76] Other locations on this chromosome have also been reported, but not confirmed.[77] Lastly, Pericak-Vance and colleagues[72] have identified a locus on chromosome 9p with linkage to AD restricted to a series of families in whom the diagnosis was confirmed by postmortem examination.

Consistent with other genes involved in AD, APOE may also act through a complex and poorly understood relation with Aβ deposition. APOE is an obligatory participant in Aβ accumulation and postmortem data indicate that isoforms exert at least some of their effects via controlling Aβ accumulation or the clearance of Aβ peptides.[78] APOE4 is associated with greater Aβ plaque density than other APOE alleles among patients with AD.[79,80] APOE-deficient mice overexpressing the human APP_{717} mutation that causes an early-onset, autosomal dominant form of AD deposit fewer Aβ plaques[81] and show greater memory impairment than wild type mice as well as mice with the APP mutation but expressing APOE.[82] A direct role for APOE independent of an interaction with Aβ involving both biochemical and neuronal integrity has been suggested in animal models with impaired memory.[82,83]

Compared with intact mice, APOE-deficient mice have lower synaptic density in cholinergic, noradrenergic, and serotonergic projections to relevant brain regions[84] and perform worse in several types of memory tasks.[82,85–87] Therefore, in animals APOE4 has a direct effect on memory in the absence of AD, and a similar effect has been observed in humans.[88]

RECENT DEVELOPMENTS IN ALZHEIMER'S DISEASE GENETICS

Aβ is the most significant known biomarker of AD. All 3 AD genes (APP, presenilin 1, presenilin 2) enhance deposition of Aβ by extracellular deposition.[89] The Aβ peptides 40 and 42 are major subtypes generated when APP is cleaved by β and γ secretase. Of the two, Aβ 42 is associated with increased risk of AD, and a number of studies support this association. Aβ 42 aggregates more rapidly and is deposited earlier,[90] and plasma levels of Aβ 42 are elevated in nondemented individuals who later develop AD compared with those who are free of AD.[91] On the other hand, Aβ 40 does not appear to alter the risk of AD.

Ertekin-Taner and colleagues[92] estimated heritability coefficients to be as high as 73% for Aβ 42 and 54% for Aβ 40. APOE did not influence the heritability estimates here, thus supporting a strong genetic influence. Further, using Aβ 42 as the phenotype, the same group identified a chromosomal region (81 cM) that explains excess Aβ in families with late-onset AD. Interestingly, two other groups reported the same chromosomal region as a candidate region when AD was used as the phenotype.[76,77]

Others are studying genetic contributions to the age at onset of AD with the reasoning that by identifying the genes controlling for onset and by finding means to delay the onset of AD, the burden on health care will be reduced and the quality of life will improve. Recently, Olson and colleagues[93] used an age-at-onset model to argue for a role of APP in late-onset AD in which it was not previously observed. Subsequently, Li and colleagues[94] reported a modest linkage to chromosome 10q for age at onset of AD. These findings will need to be confirmed.

These approaches may open new leads into the genetics of AD. The use of biomarkers like Aβ will improve the capacity of genetics as a means to understand the pathobiology of AD. Since the biomarkers represent intermediate phenotypes that are closer to the actions of the genes, the genotype-phenotype correlation is likely to be stronger than with AD, thereby enhancing power to detect genes with modest or weak effects. Further, because they provide a range of phenotype values on all family members (eg, individuals with mild cognitive impairment

as well as very old individuals who remain unaffected), the biomarkers are likely to be more informative than a simple AD diagnosis.

Apolipoprotein E

APOE has been extensively investigated because of its role in lipid metabolism and ischemic cardiovascular disease.[41,95–102] Mortality from ischemic heart disease is related to the presence of the APOE4 allele.[103] Variation at the APOE locus has also been related to cerebral hemorrhage and insulin levels.[102,104,105]

There are 3 common APOE alleles: E2, E3, and E4. APOE3 is by far the most common allele, occurring in up to 60% to 80% of humans; APOE4 is considered to be the ancestral allele. The frequency of APOE4 varies worldwide, from 40.7% among African pygmies[106] to 8.5% among individuals from Morocco. Among European populations the highest frequency of APOE4 occurs among Lapps, Swedes, and Finns, while the lowest frequency occurs in Greek and Italian populations. Sudanese, Nigerians, and African Americans have an intermediate APOE4 frequency of 22% to 29%. The lowest frequency occurs among Asians.[107]

Several different mechanisms as to how APOE affects AD risk have been suggested. APOE may lower the age at onset of AD in sporadics,[67,108] in families with individuals who have mutations in APP,[109,110] and in Down syndrome individuals.[69] Alternatively, APOE may have more immediate effects on the nervous system. For example, compared to individuals with other APOE genotypes, those with an APOE4 allele appear to develop hippocampal atrophy[111–113] and are more likely to develop age-related cognitive impairment.[88,114,115] Memory decline observed in the elderly population may well be the direct effect of APOE4 on hippocampal-based memory systems rather than incipient AD. The APOE4 variant of APOE has been shown to cause a decrease in synapse per neuron ratio,[116] developmental defects within the dentate gyrus,[117] and increased vulnerability to exogenous neurotoxins.[87] Any one of these, or other mechanisms as yet unidentified, may explain the decrease in memory over time among humans with the APOE4 allele.

Although a large number of studies have examined the potential for gene-environment interaction in AD, there is little evidence of an important environmental risk factor that interacts with APOE. Despite the important role of APOE on lipid metabolism, there appears to be no relationship between lipid levels, APOE, and AD.[118] Presence of APOE4 seems to increase the risk for dementia and AD independently of its effect on dyslipidemia and atherogenesis.[119] Smoking also increases the risk of AD, but only among individuals without the APOE4 polymorphism.[43,44] It is unclear whether individuals with an

APOE4 allele have an excess risk of having AD when they suffer a traumatic head injury.[32,34,35,120]

GENETIC DIAGNOSIS IN AD

Although the idea of genetic testing is attractive to pinpoint at-risk individuals, given the current state of knowledge it is recommended only for a small group of individuals with early-onset AD.[121–125] Currently, the accuracy, benefits, and risks of genetic testing in patients with the disease or in their asymptomatic family members have been published. These consensus groups agree on limited testing for mutations in the genes associated with early-onset familial AD: APP, presenilin 1, and presenilin 2 may be acceptable, but only with appropriate counseling.[126–130] In contrast, there has been almost universal agreement that APOE testing should not be recommend because the test does not provide sufficient sensitivity or specificity for the diagnosis.[123] However, APOE genotyping does provide valuable information in clinical studies, since it allows for the identification of at-risk individuals or those who are in the "preclinical" stages of the illness; reduces disease heterogeneity in clinical trials and epidemiological studies; allows for a better understanding of natural history of disease, with the genotype encompassing the phases of induction, latency, and detection; and provides a target for a clinical trial. These advantages may lead to more effective therapeutic regimens.

CONCLUSION

Tremendous progress has been made in the genetics of AD in recent years. Three putative genes (APP, presenilin 1, presenilin 2) and a risk-factor gene (APOE) have been identified, and several candidate chromosomal regions on chromosomes 12, 10, and 9 are now being investigated. The discovery of the relationship between APOE4 and AD led to a major advance in our understanding of the disease and its causes. Yet, these genes do not provide adequate information to apply to general clinical medicine. Future research will need to address the complex genetics of AD. To this end, some novel approaches are being introduced, including the genetics of Aβ and age at onset as phenotypes. These approaches will allow refined understanding of the genetics of AD and will lead to better screening tools and more effective therapeutic agents. Until then, genetic testing needs to be limited.✤

ACKNOWLEDGEMENTS

This work was supported by Federal Grants AG15473, AG08702, AG07232, the Charles S. Robertson Memorial Gift for Alzheimer's Disease Research from the Banbury Fund, and the Blanchette Hooker Rockefeller Foundation.

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