The Genetics of Alzheimer Disease

Current Status and Future Prospects

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Four genes involved in the development of Alzheimer disease have been identified. Three fully penetrant (deterministic) genes lead to the development of Alzheimer disease in patients younger than 60 years: the *amyloid β-protein precursor* on chromosome 21, *presenilin 1* on chromosome 14, and *presenilin 2* on chromosome 1. Together, they account for about half of this early-onset form of the disease. One genetic risk factor—*apolipoprotein E-4*—is associated with late-onset Alzheimer disease. It accounts for a substantial fraction of disease burden but seems to act primarily to lower the age of disease onset. In general, none of these genes can be easily adapted for use as a diagnostic or predictive test for Alzheimer disease. Research activity includes searching for additional genes, especially for late-onset disease, and elucidating the mechanism of action of all identified genes as part of a long-term effort to develop more effective therapeutic and preventive strategies. *Arch Neurol. 1998;55:294-296*

Molecular genetic researchers have made considerable advances in identifying the genes involved in the development of Alzheimer disease (AD), a complex and genetically heterogeneous disorder. Four genes are currently known to be involved in the development of AD: *presenilin 1* (*PS1*) on chromosome 14,[1] *presenilin 2* (*PS2*) on chromosome 1,[2] the *amyloid β-protein precursor* (*APP*) on chromosome 21,[3] and the *apolipoprotein E* (*APOE*) gene on chromosome 19.[4,5] Because the discoveries of AD genetics and the putative role of "AD genes" in genetic testing for the disease have received extensive press coverage, a better understanding of AD genetics is of interest to practitioners and their patients, particularly those with a family history of AD.

Increased concern among those with a family history of AD is warranted. Other than longevity, family history is the principal risk factor for AD. Having a first-degree relative with the disease approximately doubles the risk of AD, and age at onset tends to be correlated in families.[6] Twin studies are consistent with a genetic basis for the familial aggregation of AD and age at its onset.[7] The disorder is typically divided into early- and late-onset forms, using 60 or 65 years of age as the cutoff point. The familial pattern is easier to see in patients with the early-onset form, at least in part because most members of families with early-onset AD live through the period of risk, but it is present in families with late-onset AD as well.[8] In addition to its critical clinical and public health significance, the distinction between early- and late-onset disease has helped to tease apart the genetics of AD.

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THE GENETICS OF EARLY-ONSET AD

Initial efforts to understand the genetics of AD focused on early-onset disease, using large, multigenerational families with a clear autosomal dominant pattern of inheritance. Thus far, these efforts have led to the identification of 3 genes that, together, account for about half of all cases of early-onset AD.

The *APP* Gene

The first gene associated with early-onset AD was the *APP* gene,[3,9] in part because of its role in the formation of amyloid, which is found in the characteristic senile plaques of brains of patients with AD, and in part because of the relationship between Down syndrome (trisomy 21) and AD. However,

this gene has been found in only about 20 families worldwide. The age at onset of AD reported for individuals harboring pathogenic mutations in the *APP* gene ranges from 39 to 67 years, with some differences in mean age at onset for each specific mutation. Six different pathogenic mutations have been identified, and all 6 seem to be fully penetrant (ie, those carrying the mutation invariably develop the disease if they live through the age of risk).[10] The *APOE-4* allele (see later herein) seems to lower the age at onset and increase the amyloid burden in patients with AD with mutations in the *APP* gene.[11]

The Presenilin Genes

Roughly half of early-onset AD pedigrees have been associated with mutations in *PS1* and *PS2*, primarily in *PS1*.[10] A genome scan initially identified an AD gene on chromosome 14 in a large group of families,[12] and *PS1* was subsequently identified by "positional cloning" in the region.[1] Using families from a group of ethnic Germans whose ancestors had settled near the Volga River in Russia, the *PS2* gene on chromosome 1 was isolated based on its homology to *PS1*.[2]

To date, investigators have reported 45 different AD mutations in *PS1* but only 2 in *PS2*.[10] Virtually all of the AD mutations in *PS1* seem to be fully penetrant and are best classified as autosomal dominant "causative" gene defects.

The age at onset of AD in families with *PS1*-linked AD is approximately 45 years, with a range of 32 to 56 years; tends to be highly correlated within families; and is not affected by *APOE-4*.[13] There are systematic differences in mean age at onset related to the specific region of the gene. The mean age at onset in families with the Volga German mutation in *PS2* is 52 years, and individual ages at onset in these kindreds range from 40 to 85 years,[10] possibly related to the *APOE-4* status of the individual[14] or to other genetic or environmental factors.[15]

Of the 47 reported AD mutations in *PS1* and *PS2,* 35 have been found in single kindreds or in single patients and in no other unrelated families or patients. Thus, about 70% of all known *presenilin* mutations identified to date are genetically "private."[10] This means that new patients or families are likely to have negative results in a screen for known *presenilin* gene defects even when they are harboring a mutation in 1 of these genes (eg, families known to be linked to chromosome 14). A similar situation occurs with mutations in the *APP* gene, which are considerably rarer. Thus, with the possible exception of large families involved in genetic research projects, it is not practicable to offer genetic testing for early-onset AD.

THE GENETICS OF LATE-ONSET AD

The picture seems still more complicated for the more common late-onset form of the disease, although to date only 1 late-onset AD gene has been identified. In addition to its complex genetics, several factors contribute to the difficulty of studying genes involved in late-onset AD.[16] First, the base rate of the disorder is high and rises steeply with age, so some clustering in families may be due to chance alone, and multiple sources of disease may co-occur in a single family. Second, late-onset AD occurs near the end of the life span, and many individuals do not survive to the age of risk. Third, elderly patients are at greater risk for other causes of cognitive decline, diluting the power of genetic studies with individuals who seem to have the disease but are not actually gene carriers (phenocopies).

THE *APOE* GENE

The *APOE* gene has 3 alleles—designated 2, 3, and 4—and the *E-4* allele is associated with AD. Investigators first reported that this allele was overrepresented in early- and late-onset familial and sporadic cases in 1993,[4,5] and many other groups subsequently confirmed and extended the finding.[17-20] However, instead of acting deterministically like the 3 early-onset genes, *APOE-4* seems to act as a risk factor for the disease, especially in *APOE-4/4* homozygotes (ie, individuals with 2 copies of this allele).[20] The *APOE-4* allele is present in 20% to 30% of the general population but in 45% to 60% of patients with AD; *APOE-4/4* homozygotes constitute approximately 2% to 3% of the general population but 12% to 15% of patients with AD. Many *APOE-4/4* homozygotes remain cognitively healthy at advanced ages. For instance, in a study[20] of affected sibling pairs with the disorder, 15 *APOE-4/4* homozygotes who were older than their 2 affected siblings, often by as much as 10 years, had no evidence of AD.

Apolipoprotein E-4 seems to act primarily as a modifier of age at onset in individuals who are otherwise susceptible to AD, consistent with its documented interaction with *APP*[11] and the 5- to 7-year difference in age at onset observed among sibling pairs discrepant for *APOE-4/4* status.[20] Presumably related to this effect on age at onset, the peak effect of *APOE-4* occurs in patients in their 60s rather than in their 70s and 80s, when the disease is more common.

Because it is neither necessary nor sufficient for the development of AD at any age, 2 national panels have strongly recommended against the use of *APOE-4* as a predictive test for AD.[21,22] In addition, although the finding of an *APOE-4/4* genotype in a patient with cognitive decline may increase the probability that the patient has AD rather than another dementing disorder, the additional information is not sufficient to obviate a proper neurologic workup. Thus, *APOE* is also not recommended for use as a diagnostic adjunct outside of research protocols.[21,22]

AD GENE DEFECTS AND AD PATHOGENESIS

The brains of patients with AD contain specific neuropathologic lesions, including neurofibrillary tangles (found inside of dying neurons) and senile plaques (found in the surrounding extracellular space). At present, the most helpful clues to the role of the 4 known AD genes in the neuropathologic development of AD relate to the senile plaques, which contain a core of β-amyloid surrounded by degenerating nerve terminals and activated glial cells. For example, *APP* gene mutations were used to construct animal models for AD because, as the name "amyloid β-protein precursor" indicates, *APP* is used to form β-amyloid. As predicted, the brains of transgenic mice expressing *APP* mutations exhibit numerous classic se-

nile plaques. However, they do not show neuronal loss or neurofibrillary tangle formation.[23,24]

At a more detailed level, several lines of evidence suggest that Aβ, the major component of β-amyloid, may play a central role in β-amyloid formation. First, AD mutations in *APP* enhance the production of Aβ42, a longer form containing 42 as opposed to the typical 40 amino acids, which is associated with increased amyloid deposition. Second, plasma and fibroblasts from patients and at-risk carriers for the *presenilin* gene mutations have been shown to contain increased amounts of Aβ42.[25] Third, patients with AD and patients with Down syndrome who carry the *APOE-4* allele show an increased amyloid burden compared with those who do not carry this allele.[26] Thus, *APP* and the *presenilins* may increase the production of Aβ, and *APOE-4* may promote its aggregation and deposition.

Another more recent clue regarding the neuropathogenesis of AD comes from the observation that the presenilin proteins may promote cell death by apoptosis,[27] and apoptosis-associated fragments of *PS2* increase as a result of the Volga German AD mutation. The extent to which apoptosis plays a role in the pathogenesis of AD is unknown, but apoptotic characteristics such as cell shrinkage, increased DNA fragmentation, and altered morphologic characteristics of the nuclei of neurons have been observed in brains of patients with AD. Thus, the relationship of presenilin metabolism, apoptosis, and Aβ generation is an area of active investigation.

FUTURE PROSPECTS

In the past 15 years, remarkable progress has been made in understanding the genetics of AD, but much work remains. The more than 50 known and undoubtedly many unknown pathogenic mutations among the early-onset genes most likely account for only half of all cases of early-onset AD, which represents a small fraction of AD overall. For late-onset disease, although there is considerable evidence that genetic factors play a substantial role, *APOE-4*—the only identified late-onset gene—seems to act primarily as a modifier at age of onset and to exert its most powerful effect in patients with onset before age 70 years. Thus, the search continues for additional genes involved in the development of AD across a range of ages, especially beyond age 70 years, when the disease is most prevalent.

Meanwhile, as described herein, studies of the molecular and biochemical events associated with these 4 known genes is rapidly advancing our understanding of how these genes might act, alone or together, to bring about the development of AD. Drug development based on this growing molecular understanding of AD neuropathogenesis is in its early stages, but is expected in time to bear fruit in the form of more effective treatments for patients with AD or preventive interventions. With identification of more of the genes involved in development of the disorder, and a greater understanding of their action, AD research holds the hope of reducing or potentially eliminating the burden of this devastating disease.

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