

Genetic Epidemiology of Alzheimer Disease

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INTRODUCTION

Dementia is a major health problem in the elderly. Following an extended period of loss of personality and cognition, the disease results in a state of complete dependency. By far the most common cause of dementia is Alzheimer disease, which is clinically characterized by a gradual, progressive decline in intellectual functions (1). Psychosis, depression, agitation, and anxiety are common manifestations (2). The most frequently used diagnostic criteria for Alzheimer disease are described by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (3). The diagnosis of Alzheimer disease is considered to be probable when alternative causes of dementia are excluded (3, 4). According to the NINCDS-ADRDA criteria, a definite diagnosis is made when a probable diagnosis of Alzheimer disease is confirmed at autopsy (3). The neuropathologic characteristics of Alzheimer disease are senile plaques, neurofibrillary tangles, amyloid angiopathy, neuronal loss, as well as decreased activity of the enzyme choline acetyltransferase (5). Senile plaques are extracellular deposits of predominantly β -amyloid. Neurofibrillary tangles are intraneuronal inclusions, which are, in part, composed of abnormally phosphorylated tau protein.

The prevalence of Alzheimer disease increases with advancing age. It affects less than 1 percent of individuals aged 60–64 years, and up to 40 percent of those over age 85 years (6). Also, the incidence increases with aging, and is estimated to be 1 per 1,000

person-years in individuals aged 60–64 years and 25 per 1,000 person-years in individuals older than 85 years (7). In Alzheimer disease research, patients with early-onset are often distinguished from those with late-onset. There is, however, no uniform definition, and frequently used cut-off points are the ages of 60, 65, and 70 years. Besides age, previous head injury, depression, low educational level, atherosclerosis, and exposure to aluminum were found to be risk factors (7–9). The use of anti-inflammatory drugs or estrogens seems to decrease the risk of Alzheimer disease (7, 10). Smokers were also found to have a decreased risk in cross-sectional studies (11), but at an increased risk in a follow-up study (12).

Genetic factors play a role in the etiology of Alzheimer disease. Familial clustering has long been recognized (13), and a positive family history of dementia is one of the most consistent risk factors (14). A distinction is often made between patients with familial and sporadic Alzheimer disease. Again, there is no uniform definition of these forms of the disease. The frequently used criterion of a positive family history of dementia does not necessarily indicate genetic susceptibility. Many people in a family, and not just those individuals who are genetically predisposed, develop Alzheimer disease in old age. Also, there is significant likelihood that genetically susceptible relatives die before the onset of disease. Given these limitations, it may not be surprising that clinical manifestations of the two Alzheimer disease types appear to be similar (15, 16). However, patients with familial Alzheimer disease may have a more rapid disease progression (17) and an earlier onset than patients with the sporadic type (16).

The first step towards the localization of the genes implicated in Alzheimer disease was achieved through linkage analysis, which requires no a priori knowledge of the pathogenesis. With this technique, in large families, one can study the extent to which a localized marker allele is inherited together with a disease mutation. Several mutations have now been identified that are, by themselves, sufficient to cause Alzheimer disease (i.e., autosomal-dominant mutations). In addition, a number of genes have been studied because

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Abbreviations: ACT, α_1 -antichymotrypsin gene; APOE, apolipoprotein E gene; APP, amyloid precursor protein gene; NACP, gene for non-amyloid- β component of amyloid precursor protein; NINCDS-ADRDA, Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; PS-1, presenilin 1 gene; PS-2, presenilin 2 gene; VLDL-r, gene for very low density lipoprotein receptor.

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they code for proteins that are part of the Alzheimer disease pathology. Through this candidate gene approach, common variations in genes (i.e., polymorphisms) were identified which increase the risk of Alzheimer disease, but are, by themselves, not sufficient to cause the disease. These genes are referred to as susceptibility genes.

In this review, the genes involved will be discussed in light of their relative contribution to the development of Alzheimer disease and their putative role in the pathogenesis. First, we will consider the autosomal-dominant mutations and the susceptibility genes. Next we will review the interaction between different genes and environmental risk factors for Alzheimer disease. Finally, we will discuss the clinical and public health implications.

AUTOSOMAL-DOMINANT MUTATIONS

Amyloid precursor protein

The localization of the first gene involved in Alzheimer disease was hinted to by the observation that Alzheimer disease is very common in middle-aged patients with trisomy 21 (Down syndrome) (18, 19). As most Down syndrome patients carry three copies of chromosome 21 (instead of two), this finding indicated that overexpression of one or more genes on chromosome 21 may lead to the development of Alzheimer disease. In 1987, the gene encoding for the amyloid precursor protein (APP) was isolated and localized on chromosome 21 (region 21q11.2–21q21.2) (20). Amyloid precursor protein is the precursor for β -amyloid, a protein that accumulates in senile plaques and cerebral blood vessels in Alzheimer disease brains. Therefore, the APP gene was considered to be a candidate for Alzheimer disease despite the fact that the causal relation between senile plaque formation and the development of Alzheimer disease was an issue of debate. Arguing strongly against a causal relation was the absence of a relation between severity of dementia in Alzheimer disease patients and β -amyloid burden (21). Moreover, senile plaques can also be observed in brains from nondemented elderly (22).

In 1991, a mutation in the APP gene was identified which leads to Alzheimer disease (23). Since then, several other APP mutations have been found that cause autosomal-dominant forms of Alzheimer disease with an early-onset (24). Each of these variations change the coding for one amino acid. At position 717, three different substitutions of valine have been found: to isoleucine (Val717→Ile) (23, 25–29), to phenylalanine (Val717→Phe) (30), and to glycine (Val717→Gly) (31). Other mutations include a substitution of asparagine instead of lysine at position 670

(Lys670→Asn) (32), methionine for leucine at position 671 (Met671→Leu), and alanine instead of glycine at 692 (Ala692→Gly) (33).

It has become clear that mutations in the APP gene may explain only a limited number of patients with Alzheimer disease (34–39). The Val717→Ile mutation was found in only nine families (23, 25–29); these include families from European as well as Japanese origin, which suggests that several independent mutations may have occurred. The other APP gene mutations have been observed in one family each. Although the clinical and public health implications of these rare mutations are limited, the finding that APP mutations lead to Alzheimer disease implies that β -amyloid is most likely involved in the disease etiology. Several studies have examined the consequences of the APP mutations to the β -amyloid protein (i.e., the product of the APP gene). The consequence of the Val717→Ile mutation may be that longer β -amyloid fragments are generated, which aggregate more rapidly (40). For the Lys670→Asn and the Ala692→Gly mutations, the secretion of β -amyloid appears to be increased (41–43). Although several functions have been proposed for β -amyloid and amyloid precursor protein, their function is not yet known (44). Amyloid precursor protein resembles, on the basis of its amino acids sequence, a cell-surface receptor (45).

APP mutations are not solely related to Alzheimer disease but may also lead to other disorders. A mutation in codon 693 of the APP gene, replacing glutamic acid by glutamine (Glu693→Gln), causes hereditary cerebral hemorrhage with amyloidosis of the Dutch type, an autosomal-dominant form of hemorrhage due to amyloidosis (46, 47). The Ala692→Gly mutation results in Alzheimer disease and in cerebral hemorrhage due to congophilic amyloid angiopathy (33).

Presenilins

Since the amyloid precursor protein gene could only explain the development of Alzheimer disease in a small number of families, several groups have searched for other genes. In 1992, the second Alzheimer disease gene was localized on chromosome 14 (48). However, this gene could not be isolated until 1995 (49). It was designated presenilin 1 (PS-1) because of the presenile onset of disease in the families studied. It has been suggested that mutations in the PS-1 gene may cause up to 70 percent of all autosomal-dominant Alzheimer disease with onset before age 55 years (49–51). However, screening of a population-based sample of early-onset Alzheimer disease patients revealed PS-1 mutations in not more than 7 percent (52). At present, over 40 different mutations in PS-1 have been described (49–60). The diverse ethnic

origin of patients suggests a high frequency of new PS-1 mutations. It cannot be excluded that mutations in the PS-1 gene can also be found in Alzheimer disease patients with the sporadic form (i.e., cases with no family history of dementia). Mutations in the PS-1 gene may also lead to Alzheimer disease with a late-onset. Carriers of two type 1 alleles at intron 8, a polymorphism that is not expressed, were found to have an increased risk for the late-onset form of Alzheimer disease (61). However, this finding could not be confirmed by others (62). The exact proportion of Alzheimer disease patients that can be ascribed to PS-1 mutations has yet to be determined.

Within months after the identification of PS-1, a similar gene on chromosome 1 was localized and was called presenilin 2 (PS-2) (58). At present, two PS-2 mutations that cause Alzheimer disease have been found. PS-2 mutations appear to be a rare cause of early-onset Alzheimer disease. One of the PS-2 mutations was identified in seven families of Volga-German origin (63). The second PS-2 mutation was found in an Italian Alzheimer disease family (58).

The role of the presenilins in the pathogenesis of Alzheimer disease is unknown. The gene product of presenilin-1 is a membrane protein (51). Presenilin-1 has been found in senile plaques from Alzheimer disease patients, and not only in those with a mutation in the PS-1 gene (64). It has been suggested that a mutation in PS-1 leads to greater secretion of long β -amyloid which aggregates more rapidly (60, 65).

SUSCEPTIBILITY GENES

Apolipoprotein E

Before apolipoprotein E was found to be involved in the etiology of Alzheimer disease, apolipoprotein E had been studied because of its pivotal role in lipid metabolism (66). The apolipoprotein E gene is localized on chromosome 19 (region 19q13.2) and has three common alleles (APOE*2, APOE*3 and APOE*4) that code for three different isoforms (ϵ 2,

ϵ 3, and ϵ 4, respectively) (66). The apolipoprotein E isoforms are structurally very similar, but differ in one or two amino acids: ϵ 3 has cysteine on position 112 and arginine on position 158, ϵ 4 has arginine on these positions, and ϵ 2 cysteine (67). In populations of European ancestry, the APOE*3 allele has a frequency of 0.77. APOE*2 and APOE*4 are less common (allele frequencies, respectively, 0.08 and 0.15 in populations of European origin) (68). APOE*4 is more rare in Chinese and Japanese populations (0.06–0.12) (68), and more frequent in Africans (0.21) and in Finns (0.23) (68, 69).

Strength of association. In 1991, linkage to chromosome 19 was reported in families with late-onset Alzheimer disease (70). One of the genes located in this region is APOE. As apolipoprotein E was also found in senile plaques, APOE was tested as a candidate gene for Alzheimer disease (71). In 1993, Strittmatter et al. (71) reported that the APOE*4 allele frequency was significantly increased in familial Alzheimer disease patients derived from a brain bank (71). Since then, numerous research groups confirmed the increased frequency of the APOE*4 allele among Alzheimer disease patients (72–97). In a meta-analysis of the findings up to early 1995 (98), both early- and late-onset Alzheimer disease, as well as the sporadic and familial types, were associated with APOE*4 (table 1). However, an increased APOE*4 frequency in familial early-onset Alzheimer disease has not been reported consistently (93, 99–101). Part of the discrepancy between studies on familial early-onset Alzheimer disease can be explained by the lack of uniform criteria for familial disease.

Several studies showed that subjects with two copies of the APOE*4 allele (homozygotes) have a higher risk compared with those with one copy (heterozygotes) (odds ratios vary from 4.9–34.3 and 1.6–5.1, respectively) (72–75, 80–82, 86, 87, 91, 97). There is some evidence that the APOE genotype effects the age-of-onset of Alzheimer disease. APOE*4 homozy-

TABLE 1. APOE*4 allele frequencies in various Alzheimer disease types*

Type of Alzheimer disease	No. of studies	No. of patients	APOE*4 frequency	95% confidence interval
Early onset familial†	2	143	0.42‡	0.36–0.48
Early onset sporadic	4	168	0.28‡	0.23–0.33
Late onset familial	8	601	0.48‡	0.45–0.51
Late onset sporadic	24	1,562	0.37‡	0.35–0.39
Nondemented controls	1	2,000	0.14	0.12–0.16

* Based on meta-analysis (98).

† Cases were not examined for all currently known autosomal dominant mutations; later studies did not find an association (93, 99–101).

‡ Significantly increased relative to nondemented controls, $p < 0.0001$.

gotes were found to have an age-of-onset 3–16 years earlier as compared with non-APOE*4 carriers (73, 81, 87, 102–106). The age-of-onset effect was, however, not observed consistently (82, 96, 97, 107–109). Also, the role of the APOE*2 allele in Alzheimer disease is a matter of controversy. Several studies reported a decreased APOE*2 frequency in Alzheimer disease patients (0.01–0.05), independent of the effect of APOE*4, which suggests a protective effect (75, 92, 110–113). In contrast, others found an increased frequency of APOE*2 (0.13–0.14) (114–115).

Heterogeneity of studies. Despite the large number of investigations compatible with an increased risk of Alzheimer disease for carriers of APOE*4, the strength of this association varies considerably. The differences across studies are probably the result of the differences in ascertainment of cases (clinic-versus population-based, prevalent versus incident), the heterogeneity in case-series studied (familial or sporadic, late-onset versus early-onset) and the diagnostic criteria used (possible, probable, or definite Alzheimer disease). The large majority of studies used clinic-based patient series, and all studies except two (116, 117) are based on prevalent cases. Thus, selection may also have occurred because of referral bias and survival bias associated with the APOE genotype.

Possible bias. An important aspect regarding referral bias is that APOE may, in part, determine the symptoms of Alzheimer disease (118–120), which may effect clinical referral. Also, the fact that APOE*4 carriers more often have a positive family history of dementia (80, 91) could lead to referral bias (121). Compared with Alzheimer disease cases from a community-based study, patients from a memory clinic indeed had a higher APOE*4 allele frequency, an earlier disease onset, and a more advanced state at assessment (122).

With regard to putative prevalence-incidence bias, investigations of the role of APOE in progression and survival of Alzheimer disease are relevant. However, studies on APOE and the rate of progression of Alzheimer disease have yielded inconclusive results (102, 103, 107, 123–127). No relation between APOE and mortality has been found by some groups (109, 128), while other groups described an increased survival in Alzheimer disease patients with APOE*4 (102, 103, 114, 123) and a decreased survival for early-onset Alzheimer disease patients with APOE*2 (114). A problem in the interpretation of these studies is that each of these investigations is based on prevalent patients who may have entered the study at different stages of disease. Also, the characteristics of the Alzheimer disease patients and the definition of disease

duration varied considerably. However, if the finding that APOE*4 carriers survive longer is correct, the risk of Alzheimer disease associated with APOE*4 may be inflated in studies of prevalent patients conducted to date (129).

Incidence studies. In two population-based studies on incident patients, in which participants were included before onset of dementia, a relatively low APOE*4 frequency had been observed (116, 117). However, one of these studies focussed on dementia and not on Alzheimer disease specifically (116), which may explain, in part, the low APOE*4 frequencies observed (0.17 in patients using *Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R)* criteria (130), and 0.26 in cases diagnosed with *The ICD-10 Classification of Mental and Behavioral Disorders: Diagnostic Criteria for Research* criteria (131)). However, the other study on incident Alzheimer disease patients also reported a low APOE*4 frequency (0.13) (117), and used the NINCDS-ADRDA criteria (3). As this latter study was performed among Italian-Americans in whom APOE*4 is relatively rare, the frequency of this allele in Alzheimer disease cases was still significantly increased compared with the unaffected controls (0.08) (117). Age- and sex-specific risk estimates associated with the various APOE genotypes await large-scale incidence studies.

Causal inference: studies of different populations. An important issue to resolve is whether APOE is causally related to Alzheimer disease or whether another, neighboring gene exerts the pathogenic effect. The latter situation is known as a gene in linkage disequilibrium. Indeed, polymorphisms flanking the APOE gene have been found to be associated with Alzheimer disease in some studies (92, 93, 132). Investigations of different populations may shed light on the possibility of linkage disequilibrium. If APOE*4 is causally related to Alzheimer disease, one expects to find an association in each population studied, assuming that there are no strong effect modifiers which differ across populations. The association between APOE*4 and Alzheimer disease has been confirmed in various populations, including those of African, Chinese, and Japanese origin (133–137). However, findings in persons of African origin have been inconsistent. In a small study of Nigerians, no association between APOE*4 and Alzheimer disease was observed (69). Whereas one study in African-Americans reported that APOE*4 was a strong risk factor for Alzheimer disease similar to findings in Caucasians (133), another found a lower APOE*4 associated risk for African-Americans compared with Caucasians (134).

Causal inference: experimental studies. In spite of

the weak associations in the studies on incident cases (116, 117) and on patients of African descent (69, 133, 134), there is support from experimental studies that APOE is causally related to Alzheimer disease. It has been shown that the β -amyloid burden is related to the APOE genotype (84, 85, 96, 103, 138, 139). The apolipoprotein isoforms may have a specific effect on the formation, aggregability (140–143), or clearance (84, 144) of β -amyloid. Also, specific differences of isoforms in the binding to β -amyloid have been reported, though not consistently (145–147). The ϵ 4 isoform may bind less strongly than ϵ 3 to tau and MAP2c proteins, which may result in the development of neurofibrillary tangles (148, 149), another neuropathologic feature of Alzheimer disease. Alternatively, the transport of lipids could be compromised in APOE*4 carriers, leading to a poor reinnervation after neuronal cell loss (150). The cholinergic neurotransmitter system relies heavily on lipid homeostasis (150), and the choline acetyltransferase activity in the Alzheimer disease brain may be inversely related to the number of APOE*4 alleles (151, 152). In vitro studies suggest that ϵ 3 facilitates and ϵ 4 inhibits neurite outgrowth (153, 154). Recently, ϵ 4 has been shown to have decreased antioxidant activity, and ϵ 2 increased activity, as compared with ϵ 3 (155). Apart from structural differences between the apolipoprotein E isoforms, it was found that the apolipoprotein E content decreases with increasing number of APOE*4 allele copies in the Alzheimer disease brain (156).

Other susceptibility genes

A number of genes have been studied because of the possible role of the gene product in Alzheimer disease pathology. Like apolipoprotein E, α_1 -antichymotrypsin (ACT) binds to β -amyloid, and serves as a stimulatory factor in the polymerization of β -amyloid (142). In the Alzheimer disease brain, α_1 -antichymotrypsin is expressed particularly in areas that develop β -amyloid deposits (157). Therefore, the ACT gene was considered to be a candidate gene involved in Alzheimer disease. Although in one study homozygotes for the ACT*A allele were found to have an 1.5-fold increased risk of Alzheimer disease as compared with other subjects (158), this could not be confirmed elsewhere (159).

The association between APOE*4 and Alzheimer disease led to studies of genes whose products bind to apolipoprotein E. The very low density lipoprotein receptor (VLDL-r) is one of the receptors for lipoproteins containing apolipoprotein E (160). Subjects homozygous for the A2 allele of the VLDL-r gene had a two- to threefold increased risk of Alzheimer disease in a Japanese study (161). However, these findings

could not be verified in Caucasian populations (162, 163).

There is some evidence that the gene encoding the precursor protein of non-amyloid- β component (NACP) may be involved in the pathogenesis of Alzheimer disease. Among carriers of APOE*4, the NACP allele 2 was found to be more frequent in nondemented elderly than in Alzheimer disease patients (164). The observation that the NACP allele 2 may exert a protective effect remains to be confirmed.

The CYP2D6B allele may increase the risk of Parkinson disease and the Lewy body variant of Alzheimer disease (165, 166). The protein product of CYP2D6 is involved in detoxifying environmental toxins (167). As there are similarities between Alzheimer disease and Parkinson disease, and familial aggregation of these disorders has been observed (7), CYP2D6B was studied in Alzheimer disease. The CYP2D6B allele was found to be associated with milder synaptic pathology in Alzheimer disease brains (168). A recent study suggests that the frequency of this allele was comparable in Alzheimer disease patients and in controls (169). Therefore, the role of the CYP2D6B allele in the development of Alzheimer disease may prove to be limited.

INTERACTION OF GENES AND ENVIRONMENTAL FACTORS

As large numbers of patients and controls are needed to study rare gene-gene and gene-environment interactions, studies up until now focused on the most frequent genetic risk factor for Alzheimer disease, the APOE*4 allele. Several studies found the strongest effects of APOE*4 on Alzheimer disease to occur in those patients with a positive family history of dementia (80, 91, 96, 98, 170). However, for most dominant mutations, no interaction with APOE*4 was observed (61, 93, 99–101). The exception may be the Val717→Ile APP mutation, for which APOE appears to effect the age of Alzheimer disease onset (171, 172). Patients with APOE*2 had a later onset age (171, 172), while disease onset was earlier in cases with APOE*4 (172). It is still controversial whether there is interaction between APOE and the putative susceptibility genes ACT, VLDL-r, and NACP (158, 159, 161–164, 173).

There is some evidence that the association between APOE*4 and Alzheimer disease may be modified by gender (73, 174–176). In a study of familial Alzheimer disease, women who carry one APOE*4 allele had a similar risk of Alzheimer disease as women carrying two APOE*4 alleles (177). In men, to the contrary, no significant differences were observed between APOE*4 heterozygotes and non-APOE*4 car-

riers (103, 177). However, a gender-specific APOE*4 associated risk of Alzheimer disease was not found by other investigators (178). The interpretation of these findings is hampered by the fact that these findings are based on prevalent patients, and may be the result of gender-specific differences in cardiovascular mortality related to APOE*4 (179).

The odds ratio for Alzheimer disease associated with APOE*4 may decrease with age (75, 113, 180). In very elderly subjects, the APOE*4 frequency was similar in Alzheimer disease patients and cognitively normal individuals (181). There are several explanations possible, including age-dependent expression of the APOE gene and interaction of APOE*4 with an age-dependent factor. However, in one of the population-based studies of incident Alzheimer disease patients, the APOE*4 related risk of Alzheimer disease did not vary with age (117). Further studies of age-specific risks are clearly needed.

Serum cholesterol levels are partly determined by genetic factors, including the APOE gene (68). It has been suggested that total cholesterol level may modulate the APOE*4 associated risk of Alzheimer disease (175). Also, the presence of generalized atherosclerosis seems to potentiate the effects of APOE*4 on the risk of Alzheimer disease (8).

A previous head injury may be another environmental factor involved in the etiology of Alzheimer disease (9). A synergistic interaction was observed between the effects of traumatic head injury and APOE*4 (182). APOE*4 carriers without a previous head injury had a twofold increased risk of Alzheimer disease, while APOE*4 carriers with a head injury had a 10-fold increased risk (182). This observation was supported by a postmortem study which suggested that deposition of β -amyloid after head injury may depend on the number of APOE*4 alleles (183).

A recent study suggests that reactivation of herpes simplex virus type 1 in the brain is associated with the development of Alzheimer disease when the APOE*4 allele is present (184). If confirmed, this finding indicates another gene-environment interaction.

In several case-control studies, an inverse relation between smoking and Alzheimer disease has been reported (11). The putative protective effect of smoking may be limited to APOE*4 carriers with a family history of dementia (185). This relation should be further investigated, since previous studies have been subject to selection bias, survival bias, and recall bias. Indeed, in a recent follow-up study, smokers were found to have an increased risk of dementia, especially in the absence of APOE*4 (12).

Estrogen use during menopause may lower the risk of Alzheimer disease (10). Among women with

APOE*4, the protective effect of estrogen was stronger compared with women without APOE*4, although these differences were not statistically significant (10). In a study of Alzheimer disease patients with early-onset, the protective effect of estrogen use was found to be limited to women who carried APOE*4 (186).

Limited information is available on the interaction of APOE with the use of nonsteroidal antiinflammatory drugs. Although the strongest evidence for an association was found in persons without APOE*4, there is no significant evidence for effect modification (187).

CLINICAL AND PUBLIC HEALTH IMPLICATIONS

There are three potential applications of testing for the presence of Alzheimer disease mutations: 1) for predictive testing in unaffected individuals in order to identify persons at high risk of Alzheimer disease, 2) as a diagnostic test, and 3) to select demented patients for therapy. Despite the high risk of Alzheimer disease associated with the known dominant mutations in the APP, PS-1, and PS-2 genes, testing will be not be valuable because these mutations are very rare. Only in patients from families with an autosomal-dominant form of Alzheimer disease, screening for these mutations may be useful. This section will therefore focus on APOE*4, by far the most frequent genetic risk factor for Alzheimer disease.

Predictive testing. Many authors have argued against the use of APOE genotype in the prediction of whether or not someone will develop Alzheimer disease (188–193). An important argument is that reliable age-specific estimates of the lifetime risk are lacking. Estimates, based on data from various case-series, indicate that APOE*4 carriers have a substantial chance of *not* developing Alzheimer disease during a lifetime (192). Although there is some evidence that APOE typing can identify asymptomatic people at high risk of Alzheimer disease (194, 195), in the absence of preventive strategies, presymptomatic testing seems to be of little use and to be unethical.

Diagnosis. It has been suggested that APOE testing be used in the diagnosis of Alzheimer disease (189). Although APOE genotyping may further increase diagnostic certainty in a population of *probable* Alzheimer disease patients (196), its value in the differential diagnosis of *dementia* is limited, as APOE*4 may also be associated with other dementing illnesses (197). Increased APOE*4 frequencies have been reported in patients with vascular dementia (94, 198, 199), Lewy body disease (200–203), Parkinson disease dementia (204), frontal lobe dementia (205, 206), and Creutzfeldt-Jakob disease (207). Findings on APOE and the non-Alzheimer disease dementias are somewhat controversial however (208–214), with the

exception of Lewy body disease. The probable association between APOE*4 and the most important alternative diagnosis for Alzheimer disease, vascular dementia (94, 198, 199), may limit the utility of APOE testing in the differential diagnosis of dementia. There is an ongoing debate on this issue. The American College of Medical Genetics/American Society of Human Genetics and others did not recommend APOE testing in the diagnosis of Alzheimer disease (190). The National Institute on Aging/Alzheimer's Association Working Group concluded that physicians may choose to use APOE genotyping as an adjunct to other tests currently employed for Alzheimer disease diagnosis (191).

Therapy. It has further been suggested that APOE genotyping may be valuable in the evaluation of therapy. Tacrine, an acetylcholinesterase inhibitor (215), was found to be less effective in demented APOE*4 carriers, as compared with patients who do not carry an APOE*4 allele (151). However, in this small study, patients were selected from a group who completed the trial and who showed maximal change (151). Diagnostic criteria were not described, and it is not clear whether there were baseline differences in the stage of disease between patients with and patients without APOE*4 (151). Besides, several outcomes were used with no adjustment for multiple testing (151). This finding is, therefore, preliminary and needs to be confirmed by others.

DISCUSSION

In recent years, remarkable progress has been made in the unraveling of the genetic basis of Alzheimer disease. The possible interaction of various Alzheimer disease genes and environmental factors is schematically represented in figure 1. Yet, research on the genetics of Alzheimer disease is far from completed. Various mutations in three genes (APP, PS-1, and PS-2) have been identified which can lead to Alzheimer disease, but these are all extremely rare. The APOE*4 allele is a common risk factor, but despite the overwhelming evidence for an increased frequency of this allele in Alzheimer disease patients, there are currently no reliable age- and gender-specific risk estimates available. The risk of Alzheimer disease associated with the APOE*2 allele also remains to be resolved. Up until now, findings on other susceptibility genes have been difficult to reproduce.

It is to be expected that other, yet unknown genes are involved in the etiology of Alzheimer disease. Part of the familial aggregation in the general population or in genetically isolated populations could not be explained only by already known Alzheimer disease genes (52, 80, 91, 216, 217). The yet unknown Alz-

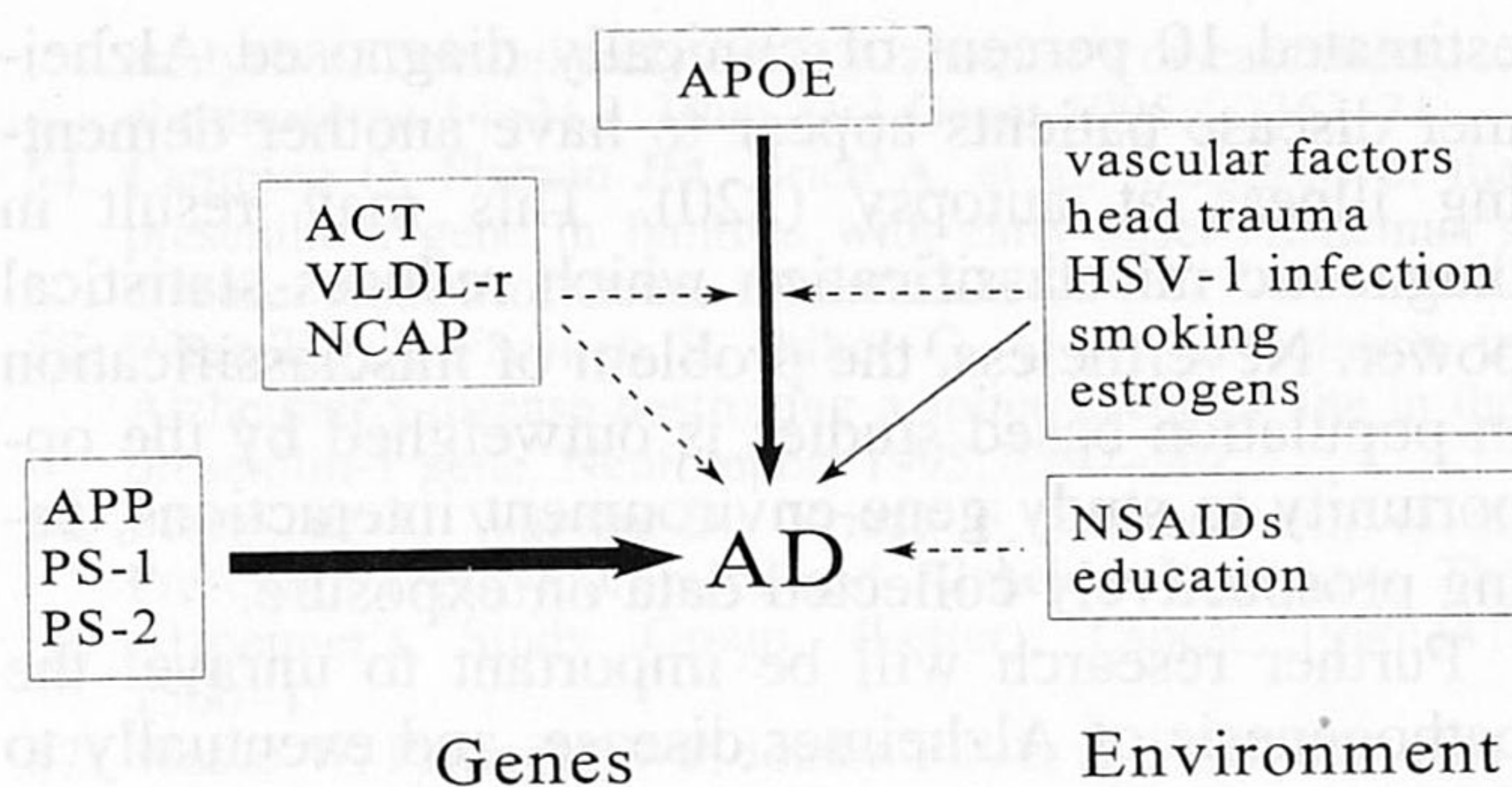


FIGURE 1. Schematic representation of various genetic and environmental factors involved in the etiology of Alzheimer's disease (AD). The boldness of the arrows indicates the evidence of a causal association. APP indicates the amyloid precursor protein gene, PS-1 the presenilin 1 gene, PS-2 the presenilin 2 gene, ACT the α_1 -antichymotrypsin gene, VLDL-r the gene for the very low density lipoprotein receptor, NCAP the gene for non-amyloid- β component of amyloid precursor protein, and APOE denotes the apolipoprotein E gene. HSV-1 indicates herpes simplex virus type 1, and NSAIDs denotes nonsteroidal antiinflammatory drugs.

heimer disease genes are most likely implicated in the etiology through more complex mechanisms than the ones identified to date.

Classic linkage analysis does not seem to be a promising technique to detect these new genes, as families with Alzheimer disease patients in multiple generations are rare and linkage analyses did not yield clues (48). An alternative approach is to examine affected sib-pairs, but this requires a large number of siblings (218). In recent years, much attention has been paid to the possibility of localizing disease genes using case-series instead of families (218). The statistical power of these studies in the general population is limited, but the situation is more favorable in isolated populations where there is usually less genetic variability (219). However, extrapolation of these findings to the general population may be limited. As experimental research will identify more and more details of the protein chemistry of Alzheimer disease, and the Human Genome Project advances further in identifying genes, the opportunities for candidate-gene studies will increase. However, all of the above techniques for the identification of new genes are subject to false-positive findings. As there is usually no a priori hypothesis as to which allele is associated with the disease, and a large number of alleles can be tested, problems related to multiple testing are encountered.

An important aim in genetic-epidemiologic research will be to determine the contribution of newly identified genes to the occurrence of disease. For this purpose, population-based studies are needed in order to overcome referral bias. The problem of survival bias can only be overcome in a follow-up setting. However, in such surveys it has been difficult to implement neuropathologic confirmation of the diagnosis. An

estimated 10 percent of clinically diagnosed Alzheimer disease patients appear to have another dementing illness at autopsy (220). This may result in diagnostic misclassification which reduces statistical power. Nevertheless, the problem of misclassification in population-based studies is outweighed by the opportunity to study gene-environment interactions, using prospectively collected data on exposure.

Further research will be important to unravel the pathogenesis of Alzheimer disease, and eventually to develop effective therapy. Transgenic animals carrying Alzheimer disease mutations can be useful for this purpose. Given the developments in pharmacology and genetics, it is likely that genetic testing will be used to identify subgroups that will benefit from new therapeutic interventions. For susceptibility genes, unraveling interactions with preventable risk factors may ultimately lead to a new area in genetic epidemiology, prevention of Alzheimer disease in genetically susceptible groups.

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