Guest Editorials

Susceptibility Genetics in the Etiopathogenesis of Alzheimer’s Disease: Role for Potential Confounding Factors

Finding genetic linkage and identifying the genes responsible for disease can revolutionize our understanding of disorders with obscure or complex etiology and pathogenesis (Weatherall, 1991). When relevant genes have been cloned, the identification of specific mutations that cause disease (Goate et al., 1991) enables molecular pathogenesis of the condition to be addressed.

The known genetic causes of Alzheimer’s disease (AD), which include mutations in the APP gene and two presenilin genes, are rare and account for approximately 5% to 15% of all cases (Tanzi et al., 1996). These rare mutations are transmitted as autosomal dominant traits. In contrast, the majority of cases of AD are sporadic and generally of late onset, occurring after 65 years of age. Although much can be learned from the studies of mutations in the APP and presenilin genes, the molecular basis of sporadic AD is more complex. Whereas single gene defects that exert a major effect are rare but specific causes of AD, the majority of cases probably arise as the result of several polygenes, each making a comparatively small contribution toward the phenotype. Two main strategies exist for identifying candidate genes. The first is to perform linkage analysis based on AD pedigrees. The second is to carry out association studies on samples from the general population. The latter approach was used to identify apolipoprotein E polymorphisms (APOE, gene; apoE, protein) as a risk factor for AD. Other irregular patterns of transmission can be observed. These include mitochondrial inheritance, genomic imprinting, and so-called dynamic mutations that lead to the phenomenon of anticipation, as observed in Huntington’s disease.

Allen Roses (1997) reviewed the findings with APOE in the context of the pathogenesis of AD. Much remains, however, to be understood about those variables that may contribute to the central pathological changes of AD, namely neuritic plaques and neurofibrillary tangles. In this article, we discuss this in detail with special reference to the APOE polymorphism and potential confounding factors.

APOLIPOPROTEIN E AND ALZHEIMER’S DISEASE

An association between the apolipoprotein E ε4 allele and AD was first demonstrated by Strittmatter and colleagues (1993).
Whereas linkage represents a relationship with a specific chromosomal locus, association is a relationship between common functional variations (allelic polymorphisms) in a susceptibility gene that is present in the general population. Although there may be some minor ethnic variations (Hendrie et al., 1995; Maestre et al., 1995), similar APOE genotype distribution for patients with AD in populations of diverse ethnic backgrounds suggests that it is the ε4 allele that is directly responsible for its association with AD. A decreased risk of AD in those with an ε2 allele suggests that it is due to the APOE gene rather than a nearby gene in linkage disequilibrium. Tests for association between particular polymorphisms and disease phenotype require large numbers of unrelated affected patients. Although many studies have now confirmed the APOE association in AD, testing populations for APOE genotype cannot be used to predict development of AD; presence of the ε4 allele is neither necessary nor sufficient to cause disease. Furthermore, it should be noted that distribution of the ε4 allele varies considerably among different populations (Utermann, 1994).

ApoE is a plasma protein that is involved in cholesterol transport. The APOE ε4 allele is overrepresented in AD patients with late-onset symptoms, and APOE genotype represents an important biological marker for the disease, accounting for 45% to 60% of the genetic component of AD (Nalbantoglu et al., 1994).

Possible biological explanations for the association of APOE genotype with AD have included isoform-specific neurotoxic and/or neuroprotective effects of apoE and the binding of apoE to Aβ or tau proteins in an isoform-dependent fashion (Strittmatter et al., 1994). Alternatively, apoE might influence neuritic outgrowth: Whereas apoE3 stimulates outgrowth in cell culture, apoE4 has the converse effect (Nathan et al., 1994). At present, however, these explanations remain hypotheses whose relevance in vivo has yet to be established.

Before these hypotheses can be proven, a number of issues need to be addressed and which are discussed below. First, the specificity of the association between APOE genotype and various neurodegenerative, neurological, and psychiatric disorders remains uncertain. Second, does APOE genotype affect the pathology of AD? Third, are there any genetic interactions with APOE genotype? Finally, to what extent does apoE influence nonspecific factors that may or may not affect the development or progression of disease? With respect to the latter, particular concern is given to the role of cerebrovascular diseases and how they might impinge on the development of AD and its association with the APOE4 genotype.

SPECIFICITY OF THE APOLIPOPROTEIN E ASSOCIATION

Possession of an APOE ε4 allele is neither necessary nor sufficient for the development of AD, and the lifetime risk of AD in patients with an ε4 allele remains less than 1 in 3 for those without a family history of dementia (Seshadri et al., 1995). In addition to AD, the APOE ε4 allele is overrepresented in vascular dementia (see below), Pick’s disease (Farrer et al., 1995), sporadic frontal lobe dementia (Stevens et al., 1997), and dementia with Lewy bodies (Galasko et al., 1994; Harrington et al., 1994). These findings suggest that apoE4 can influence the risk of dementias that
have clearly distinct pathogenesis and patterns of clinical expression. Thus there is still uncertainty over the specificity of the APOE effect. Likewise, results from a population-based study indicated that the prevalence of dementia in E4/E4 homozygotes by the age of 90 years reached only 50% (Henderson et al., 1995), emphasizing that apoE4 is insufficient on its own to cause either dementia or AD. AD is associated with substantial neuronal loss and up to 65% of cortical neurons may die. There has not been a detailed study in which the influence of APOE genotype on neuronal loss has been studied in AD, in other neurodegenerative or psychiatric disorders, or in normal mental aging. This is important in relation to the purported specificity of the APOE association. The mechanism by which APOE exerts its influence on AD is not known. A consistent increase in the deposition of Aβ that is linked to increasing e4 gene dosage (Gomez-Isla, 1996; Polvikoski et al., 1995; Rebeck et al., 1993), that is not due to a differential survival effect (Corder et al., 1995). Duration and progression of AD are not related to APOE4, suggesting that the higher Aβ load is not a major determinant of the course of the disease. This is consistent with better correlations that are observed between cognitive impairment and neuronal loss, neurofibrillary pathology, and synapse loss (Arriagada et al., 1992; Terry et al., 1991; Wilcock & Esiri, 1982). The marked synaptic pathology in AD does not differ between patients with and without the e4 allele (Blennow et al., 1996) and there is no correlation between overall levels of apoE and synaptophysin-immunoreactivity or amyloid load in the brain (Pirttilä et al., 1996b). Evidence to provide a link between neurofibrillary pathology and APOE4 (Nagy et al., 1995; Ohm et al., 1995; Sparks et al., 1996) has not been established by others (Harrington et al., 1994; Landén et al., 1996; Rebeck et al., 1993; Sparks et al., 1996). Furthermore, patients with dementia with Lewy bodies, whose brains are characterized by minimal neurofibrillary pathology, share a similarly elevated e4 allele frequency with that observed in AD (Harrington et al., 1994; Morris et al., 1996).

If apoE had a general role in the central nervous system (CNS) response to injury, then it would be predicted that APOE genotype may affect the onset or course of neurodegenerative disorders other than AD or acute CNS trauma. APOE4 is not associated with Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, Down's syndrome, or hippocampal dementia. However, it may serve as a risk factor in the recovery from head trauma (Nicoll et al., 1995; Sorbi et al., 1995) and APOE4 is associated with a poor outcome following intracerebral hemorrhage (Albers et al., 1995). Recovery following coronary bypass surgery is influenced also by a variety of factors including APOE genotype.

Depressed people often show a non-specific cognitive impairment that, in general, responds to treatment. Krishnan and colleagues (1996) found an association between APOE4 and depression. Steffens and colleagues (1997), in contrast, reported that a history of late-onset depression was a risk factor for AD but that it was independent of APOE genotype. Similarly, elderly depressed patients with cognitive impairment are more at risk of developing AD by an APOE4-independent pathway than patients with psychotic symptoms (Zubenko et al., 1996). APOE4, therefore, may be either a risk factor for psychotic de-
pression in late life or the symptoms may represent an early manifestation of AD. Some studies have reported that APOE genotype distribution is altered in patients with schizophrenia, but the findings have been contradictory. APOE4 was decreased in patients with late paraphrenia (Howard et al., 1995), increased in schizophrenic patients (Harrington et al., 1995), and associated with a younger age of onset of schizophrenia in an elderly population in which Alzheimer pathology was increased to an extent that remained insufficient to confer a diagnosis of AD (Arnold et al., 1997). In these studies, it is likely that the complex genetics and imprecise diagnosis of schizophrenia contributed to the apparent discrepancies.

APOE GENOTYPE AND ITS INTERACTION WITH OTHER GENES

Mutations in the APP gene (Goate et al., 1991) and in two presenilin genes (Levy-Lahad et al., 1995; Rogaev et al., 1995; Sherrington et al., 1995) are sufficient to cause AD in the familial forms of the disease. To date, 56 independent mutations, which segregate with AD, have been reported in these three genes. Nonetheless, a genetic cause in perhaps as many as half of the early, familial AD cases has yet to be found (Tanzi et al., 1996). Although some of these mutations are associated with minor differences in clinical presentation, the pathological changes at autopsy remain relatively constant. The major differences are observed in age of onset and rate of progression of the disease. In contrast, and as described by Allen Roses (1997), APOE is a susceptibility locus: Each dose of ε4 increases the risk and lowers the age-of-onset distribution.

APOE genotype appears to have no effect on the phenotype of PS1 mutations (Tanzi et al., 1996). This is in contrast to the situation with APP, where APOE genotype appears to affect both age of onset and the degree of amyloid burden in carriers with APP mutations (Sorbi et al., 1995).

An explanation is needed for the absence of any APOE4 homozygotes in Down’s syndrome (Van Gool et al., 1995), a family history of which serves as a recognized risk factor for AD. It could be due to decreased survival, embryonic lethality, or some other unidentified factor. Elderly patients with Down’s syndrome develop AD pathology and frequently become demented.

Clarification of the overall effect of APOE genotype on survival is essential. Although absence of the ε4 allele is associated with longevity (Schächter et al., 1994), it is still important to study those genotypes associated with longevity alongside disease-specific analyses, as discussed by Galinsky and colleagues (1997).

Associations between other genetic polymorphisms and AD, e.g., α-antichymotrypsin (Kamboh et al., 1995), very-low-density lipoprotein receptor (Okuizumi et al., 1995), and the putative protective effect of a nonamyloid component precursor polymorphism (Xia et al., 1996) have not been established in subsequent investigations and so the role of such factors remains equivocal. Whether they play a role in a subset of AD patients cannot be excluded. Recent evidence indicates that the K variant of butyrylcholinesterase, or a nearby gene on chromosome 3, acts in synergy with APOE ε4 as a further susceptibility locus for late-onset AD (LOAD) (Lehmann et al., 1997). The possibility that mitochondrial DNA mutations may be associated with a subset of AD (Hutchin
Susceptibility Genetics in the Etiopathogenesis of AD & Cortopassi, 1995) suggests that these may affect the bioenergetic capacity of neurons (Wallace, 1994). Recently, mutations in mitochondrial cytochrome c oxidase (CO) genes CO1 and CO2 have been shown to segregate with late-onset AD and these are genes that are defective in the AD brain (Davis et al., 1997). These genes are maternally inherited, but there is no evidence that they are influenced by APOE genotype (Davis et al., 1997).

The extent of the $\varepsilon 4$ effect is diminished in the very elderly (Rebeck et al., 1994; Sobel et al., 1995) and many can reach old age without cognitive impairment despite the inheritance of one or two APOE $\varepsilon 4$ alleles (Hyman et al., 1996). Use of APOE genotype in predictive test situations, however, requires absolute risk information that can be obtained only from prospective cohort studies, a number of which are under way (Brayne et al., 1996; Feskens et al., 1994; Henderson et al., 1995; Hyman et al., 1996; Kuusisto et al., 1994; Myers et al., 1996; Petersen et al., 1995). Increased periods of follow-up investigation and information in the elderly need to be addressed further. However, the effect of APOE genotype on cognitive function in early life also merits consideration in light of recent results from a study of octogenarian twins. The findings indicate that the genetic contribution to general cognitive ability is fairly constant throughout life (McClearn et al., 1997). In this respect, it will be of interest to discover the variety of genes that contribute to cognitive ability and how each of their products interacts with each other or with apoE in both normal aging and AD.

Roses (1997) has described the need for clinicians to understand the diagnostic and predictive uses for susceptibility genes that are not the sole determinant for disease. He emphasized that these are not the same as tests for specific mutations that might cause disease. Although this is true for many complex disorders, including AD, due caution needs to be exercised in understanding the mechanism by which and to what extent particular susceptibility genes determine the course of the disease. If further susceptibility genes are to be identified, it is even more important that potential confounding factors are addressed. The mechanisms by which susceptibility factors exert their effect on AD may provide therapeutic approaches both at the molecular level and, perhaps, in the area of dealing with avoidable or treatable risk factors that become apparent through appropriate case-control, risk-assessment studies.

**CONFounding FACTORS IN SUSCEPTIBILITY POLYMORPHISMS**

Another major issue concerns the full scope of confounding factors that might be influenced by APOE genotype. A list of potential factors that may or may not influence the progression and development of AD is shown in Table 1. Although some of these factors have been considered in relation to APOE genotype (e.g., gender, age, head trauma, and others), more have yet to be examined. The factors listed have been split into three categories. Numerous biological factors may influence AD and some of these are discussed later.

Sociological factors may be directly relevant to AD or might act as surrogate markers of some other process with a genetic component (e.g., educational level may reflect intellect, a complex phenomenon with a substantive genetic input).
TABLE 1. Putative Risk Factors That May Confound the Influence of APOE Polymorphism on Development and Progression of Alzheimer’s Disease

<table>
<thead>
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<th>Biological</th>
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<tr>
<td>Family history of dementia or Down’s syndrome</td>
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<td>Increased age</td>
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<td>Late maternal age</td>
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<td>Gender/estrogen</td>
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<td>Ethnicity</td>
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<td>Hyperthyroidism</td>
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<td>Cardiovascular and cerebrovascular disease</td>
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<td>Respiratory disease</td>
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<td>Hypertension</td>
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<td>Depression</td>
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<td>Diabetes mellitus</td>
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<td>Autoimmune diseases; rheumatoid arthritis</td>
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<td>Osteoporosis</td>
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<td>Renal disease</td>
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<td>Carcinoma</td>
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<td>Sociological</td>
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<td>Level of education</td>
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<td>Environmental</td>
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<td>Head trauma</td>
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<td>Smoking</td>
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<td>Pharmacological treatments</td>
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<td>Infectious diseases</td>
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<td>Heavy metal exposure</td>
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<td>Aluminum</td>
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Note. Inclusion of items on this list does not necessarily indicate that it is an established risk factor for Alzheimer’s disease.

The strongest evidence that nongenetic, environmental factors are involved in AD comes from the observation that some monozygotic twin pairs, including shared ε4 alleles, have remained discordant for AD for up to 20 years (Breitner et al., 1995). In certain instances, the identification that such confounding factors are involved would offer the possibility for preventive and/or therapeutic intervention. Thorough analysis of all diseases associated with AD at death and during life needs to be performed in prospective epidemiological surveys. AD is associated frequently with somatic disease at death: Two thirds of patients with brains severely damaged by AD had suffered significant cardiac disease, chronic bronchitis, or other ill health during life (Blessed, 1984). Such disorders have not been systematically investigated in relation to APOE status. Furthermore, it is not known how individual diseases may affect the duration of AD or an individual’s life expectancy. APOE genotype does not affect the progression or duration of cognitive impairment or AD (Corder et al., 1995; Growdon et al., 1996; Kurz et al., 1996). To elicit an answer to such questions requires comparative studies of the development or progression of AD in those patients with and those without an ε4 allele. This presents a daunting task for which adequate sample sizes are essential (Smith & Day, 1984). Many conflicting reports, based upon small sample numbers, have appeared over the last 4 years in connection with the association between various disorders and APOE genotype distribution. Extensive multicenter epidemiological studies would be one way to address this issue.

CEREBROVASCULAR AND CARDIOVASCULAR DISEASE

Vascular dementia accounts for up to 25% of dementia cases. It is a complex concept because of the diverse vascular mechanisms that can lead to cognitive impairment (white-matter lesions, restricted cerebral blood flow, cerebral amyloid angiopathy [CAA]) and difficulties in the differential diagnosis of AD and vascular dementia. Cerebrovascular disease and vascular dementia are associated with an overrepresentation of the ε4 allele (Frisoni et al., 1994; Myers...
et al., 1996; Noguchi et al., 1993; Slooter et al., 1997). Some studies, however, have failed to confirm this association (Bétard et al., 1994; Scacchi et al., 1995; Higuchi et al., 1996; Pirttilä et al., 1996a; Sulkava et al., 1996). In a community-based study, cerebrovascular disease and APOE4 appeared to have a synergistic effect on cognitive decline in the elderly (Kalmijn et al., 1996).Isoe and colleagues (1996) reported an overrepresentation of the ε4 allele in AD and vascular dementia, but not in the nondemented patients with cerebrovascular disease. This suggests that APOE can influence the development of dementia (not specifically AD) independently of any effect on the development of atherosclerosis. Data from a recent cross-sectional population study indicate that atherosclerosis is associated not only with vascular dementia, but with AD as well (Hofman et al., 1997). An interaction between atherosclerosis and APOE genotype was also found: Increased prevalence of AD with atherosclerosis was most pronounced in those possessing an ε4 allele (Hofman et al., 1997).

Epidemiological data on vascular dementia are, however, both sparse and of poor reliability (Rocca et al., 1991). Rigorous pathological confirmation is rarely available. In general, strokes that contribute to more than 80 cm³ loss of brain tissue lead to vascular dementia. However, it is unclear to what extent small-vessel damage contributes to or exacerbates the development of AD. Alzheimer pathology may be directly linked to microvascular changes: Amyloid deposits in leptomeningeal and cortical arterioles may result in leakage (Esiri, 1994).

The ε4 allele is a significant factor in development of CAA in AD and in dementia with Lewy bodies (Kalaria & Premkumar, 1995; Lippa et al., 1995), and a high proportion of ε4 carriers with AD have severe arteriosclerosis (Kalaria, 1997). The ε4 allele is also a risk factor for CAA, independent of its association with AD (Greenberg, 1995). Nicoll and colleagues (1997) provide evidence for further complexity. These authors found that the APOE ε2 allele, but not the ε4 allele, served as a risk factor for cerebral hemorrhage due to CAA. CAA causes 10% to 15% of cases of spontaneous cerebral hemorrhage in the elderly, and it was suggested that the ε2 allele may act as a risk factor for the rupture of amyloid-laden blood vessels. This study also demonstrates that, despite similarities in the vascular deposition of Aβ in CAA and AD, the former shows important differences from AD need to be understood.

The extent of increase in the ε4 allele frequency in vascular dementia is not as great as that observed in AD but is nevertheless comparable with the statistically significant increases observed for coronary artery disease in nondemented adults (Cumming & Robertson, 1984; Davignon et al., 1988; Kuusi et al., 1989; Van Bockxmeer & Mamotte, 1992). Thus cardiovascular disease needs to be taken into consideration in addition to vascular disease that affects the brain.

Estrogen is a gender-specific factor that may modify genetic influences. Previous reports have suggested that estrogen replacement therapy may exert a protective effect on the risk of women developing AD (Henderson, 1997). Reduced penetrance of AD in men may reflect confounding relationships between cardiovascular disease and APOE4. Inheritance of APOE4 confers risk of ischemic heart disease in middle-aged men (Cumming & Robertson, 1984) but not in the elderly (Kuusisto et al., 1994), and APOE4
is less frequent in men than in women. The maximum effect is observed below the age of 70 years. In one study, 15 unaffected E4/E4 homozygous subjects were older than their affected siblings (Blacker et al., 1997). These findings may account for the higher age-specific prevalence of AD in women.

POLYGENIC INTERACTIONS

The APOE polymorphism provides one susceptibility gene for AD. Tanzi and colleagues (1996) and the team at Duke University (Larkin, 1997) have identified a second susceptibility gene for AD that is located on chromosome 12, which reaffirms that AD is both a complex and heterogeneous disorder. Whether other susceptibility genes are yet to be identified remains to be found.

In a recent preliminary study, the frequency distribution of certain HLA-DR antigen types has been reported to differ between patients with late-onset AD and controls (Curran et al., 1997). This was only evident in the absence of APOE ε4 alleles. Whereas the combined frequencies of DR1, 2, and 3 accounted for 67% of the total DR antigens in the AD group, they only represented 28% in the control group. DR4 and 6 were present at a lower frequency in AD. Although the findings of this study need to be replicated, it suggests that DR antigen type may serve as a susceptibility factor for AD and, in particular, in those patients not influenced by APOE ε4 genotype. Furthermore, it is possible that the HLA-DR association may account for the inverse association that has been reported between rheumatoid arthritis and AD; rheumatoid arthritis is associated with frequencies of 60% to 70% for the DR4 allele. A simplified scheme to represent these interconnecting factors is shown in Figure 1. As depicted, a clear APOE4-dependent distribution is suggested by the data. Studies in which APOE genotype is not taken into consideration (e.g., those undertaken prior to 1993) are liable to give erroneous findings if the factor under consideration is either dependent upon or independent of a specific APOE genotype. In the example shown, LOAD patients with the ε4 allele might mask the HLA-DR/AD association.

Payami and colleagues (1997) reported that the HLA-A2 allele is associated with an earlier onset age of AD in excess of that conferred by the APOE ε4 allele. Further studies are needed to confirm these findings and to determine whether the association is with the HLA gene or another nearby gene in the chromosome 6p21.3 region. The possible association of AD with HLA antigens would support roles for the immune/inflammatory response being involved in AD (Breitner, 1996).

COMORBIDITY

Many illnesses might contribute significant, though small, contributions to the development of AD. A number of these have been listed in Table 1 and some are found with regularity in patients with AD who undergo autopsy. Concomitant ill health and AD need to be studied further. Inconclusive results for the association between diabetes and AD (Finch & Cohen, 1997; Leibson et al., 1997) may reflect problems involved in analysis and difficulties in diagnosis. Type I insulin-dependent diabetes mellitus involves autoimmune destruction of pancreatic islets and is associated with HLA-DR3 and -DR4 anti-
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gens (Todd et al., 1987), whereas the more frequent, adult-onset type II disease shows no HLA association.

Data suggest that the ε4 allele may be protective against the development of adenoma and carcinoma of the proximal, but not distal, colon (odds ratio = .35; Kervinen et al., 1996). Whether APOE influences CNS tumors is not known.

Figure 1. Interaction between genetic and environmental factors in Alzheimer's disease (AD). This scheme represents the association between HLA-DR antigens and late-onset AD and how this might relate to APOE genotype and exposure to NSAIDs. Associations are given as odds ratios (OR), taken from Breitner (1996) and Curran and colleagues (1997). An OR greater than 1.0 represents a positive association and that below 1.0, an inverse association. The arrows point to associations between genetic polymorphisms (HLA-DR or APOE) and disorder (AD or RA) or treatment (NSAIDs). The arrows that do not penetrate the LOAD circle indicate that the inverse association with RA is not dependent on APOE4 genotype. Dotted lines indicate that the NSAIDs' effect shows a tendency to be associated with the protection of patients without an ε4 allele. Therapeutic trials with NSAIDs are still in progress. This simplified scheme does not take into account other potential confounding factors but serves to demonstrate the complexity of possible interactions between genetic and nongenetic factors that may affect the risk of developing AD. In this example, it is difficult to discern whether the inverse association between AD and RA is due to use of NSAIDs, to the HLA-DR polymorphism, or to a combination of both. NSAID = nonsteroidal anti-inflammatory drug; RA = rheumatoid arthritis; LOAD = late-onset AD.
NONGENETIC ENVIRONMENTAL FACTORS

One outcome from the discovery of susceptibility genes is, paradoxically, to assist investigations of environmental factors. Thus in studies of nongenetic risk factors, a knowledge of APOE status may shed light on how we can alter the environment to reduce the incidence of disease. As an example, a potential role of herpes simplex virus (HSV) in the etiology of AD was reported to be dependent on APOE genotype (Itzhaki et al., 1997). The combination of HSV1 in brain and possession of an ε4 allele presented a strong risk factor for AD, whereas neither of these factors on their own conferred a significant risk.

Evidence for joint effects of genes and the environment is starting to emerge. Possession of an ε4 allele acts synergistically with head trauma (Katzman et al., 1996; Mayeux et al., 1995) in a situation where increased Aβ deposition in the brain occurs. Head injury is also associated with an unfavorable outcome in patients with an ε4 allele (Teasdale et al., 1997). An inverse relationship between a history of smoking and early-onset AD cannot be explained by increased mortality in E4 carriers who smoke. The association is strongly modified by the presence of an ε4 allele: Among carriers of this allele with a family history of dementia, subjects with a history of smoking had a strongly reduced risk of early-onset AD (odds ratio .10; Van Duijn et al., 1995).

Drug treatment may be relevant to genetic polymorphisms in two respects. In relation to treatment of AD, patients that showed a poor response to tacrine were predominantly those possessing an ε4 allele (Poirier et al., 1995). The administration of other pharmacological agents may affect processes that occur in both AD and non-AD patients. Neuroleptics are associated with a greater rate of cognitive decline in AD patients, and it is the E4 carriers who seem particularly susceptible to their effects (Holmes et al., 1997). These observations indicate that APOE genotyping may prove a useful adjunct to therapeutic trials.

CONCLUSIONS

The discovery of mutations in the APP gene and genes for two presenilin proteins that co-segregate with disease in the early-onset forms of AD has provided great advancement toward our understanding of the etiopathogenesis of AD. Nonetheless, the mechanism by which these altered proteins cause AD remains speculative at present. Genes that have a major contribution to the pathogenesis of sporadic late-onset AD are likely to play a crucial role in the development of all forms of AD. The revelation that APOE genotype provides one such susceptibility factor provides a major step forward. Possession of an APOE ε4 allele, however, is neither sufficient nor necessary for AD. It is necessary to establish the disease specificity of the APOE association and to take into account as many factors as possible that may confound the analyses. Although APOE4 is an important genetic risk factor for AD, it accounted for only a small fraction of disease occurrence in a recent population-based study (Evans et al., 1997). If the ε4 allele had not had any effect in this study, then the incidence of AD would have decreased only by less than 14%. Thus it is important that extensive prospective epidemiological studies be performed to assess the interaction between susceptibility genes for AD together with genes that predispose to comorbidity in AD and en-
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environmental risk factors. As and when other risk factors are identified, their contribution can be assessed both in isolation and in combination with other risk factors. The findings from such investigations will benefit strategies for both preventive and therapeutic treatments for AD.

Alzheimer-type pathology, and neurofibrillary tangles in particular, are changes that are significantly correlated with dementia. The extent to which other genetic or nongenetic variables contribute to the central pathological changes in AD needs to be determined. A knowledge of the order of importance of such variables will hopefully give us a better understanding of the neurodegenerative processes involved in AD.

REFERENCES


Hiiguchi, S., Arahi, H., Nakagawa, T., Muramatsu, T., Sasaki, H., et al. (1996). The apolipoprotein E gene in Binswanger’s disease and...
vascular dementia. Clinical Genetics, 50, 459-461.


The frequency of apolipoprotein E4 allele is not increased in patients with probable vascular dementia. Acta Neurologica Scandinavica, 93, 352-354.


Sparks, D. L., Scheff, S. W., Liu, H., Landers, T., Danner, F., et al. (1996). The increased density of senile plaques (SP), but not neurofibrillary tangles (NFT), in non-demented
individuals with the apolipoprotein E4 allele: Comparison to confirmed Alzheimer’s disease patients. *Journal of the Neurological Sciences*, 138, 97-104.


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