Journal of Molecular Neuroscience

ISSN0895-8696/04/23:157–165/$25.00

ORIGINAL ARTICLE

APOE Genotype Effects on Alzheimer's Disease Onset and Epidemiology

J. Wesson Ashford*

Stanford/VA Alzheimer Center, Palo Alto, CA 94304–1207

Received May 29, 2003; Accepted February 4, 2004

Abstract

The risk of developing Alzheimer's disease (AD) is tied most closely to age and appears to follow Gompertzian kinetics. However, specific genetic factors are also linked closely to AD, and the apolipoprotein E *(APOE)* genotype accounts for as much of 50% of the attributable risk for AD in many populations. This paper reviews the onset, diagnosis, and epidemiology of AD, specifically with regard to the *APOE* genotype and the interaction of the genotype with age.

Index Entries: Alzheimer's disease; dementia; genetics; apolipoprotein E; Gompertz; aging; epidemiology.

Introduction

In the investigation of a disorder such as Alzheimer's disease (AD), the first step is to define the disease presentation and course clinically. The second step is to investigate the epidemiology. The third step is to understand the pathophysiology. These steps lead to the fourth step, which is to determine causation. These efforts culminate in the fifth step—the development of approaches to treatment and prevention. (For a more complete discussion on genetics of AD, *see* Ashford and Mortimer, 2002.)

Definition of AD

Alzheimer's disease (AD) has been defined clinically as a disease that causes a dementia with an insidious onset and slowly progressing course. The progression through the early, middle, and late stages of the disease is well defined (Ashford et al., 1998a). Based on its clinical pattern, AD can best be conceptualized as a disease that fundamentally affects memory storage processing. Analysis of its attack on the mind and brain suggests that it is most basically a disease of neuroplasticity (Ashford and Jarvik, 1985; Ashford et al., 1998b; Mesulam, 1999; Arendt, 2001).

It was recognized early on that AD has a significant relationship with family history. In some cases, with a very young age of onset, there is a clear autosomal-dominant transmission. However, the complexities of disease onset in older age ranges and what we now know to be a multitude of complex genetic interactions have made the cases associated with an older age of onset difficult to relate to specific inheritance patterns.

Recognition of AD onset also has been particularly difficult. That difficulty has been clearly demonstrated by the recent efforts to describe mild cognitive impairment (Petersen et al., 1999). To study the epidemiology of AD, it is critical to define the onset of the disease. The definition of the time of onset is crucial for measuring both incidence and prevalence.

The most common approach to estimating AD onset is to ask individuals who have known the

*Author to whom all correspondence and reprint requests should be addressed. E-mail: ashford@stanford.edu

patient when they first became aware of any of the symptoms that subsequently developed into the dementia. Most commonly, the first recollection pertains to a memory failure 1 to 2 yr before a clinician was consulted about the problem. However, other symptoms such as anger, depression, anxiety, or inattention might be the symptoms first recalled. In Alzheimer's original case, the first symptom was paranoid ideation, an accusation of spousal infidelity. The patient with poor memory frequently has no awareness of the problem and cannot be relied on to estimate onset. Even the recollections of the family are not necessarily reliable. Therefore, it is helpful to obtain information from any other available source, especially the notes of a treating clinician, which may reveal a concern about memory that antedates the family's recollections of their own concerns. Because of the unreliability of this historical inquiry, further estimation of onset might be made with the use of objective tests such as the Mini-Mental State Exam (MMSE) (Folstein et al., 1975) or functional brain scans (Ashford et al., 2000). From these objective measures, using an estimate of average disease course, approximations of disease onset might be calculated back in time (Ashford et al., 1995; Shih et al., 2001).

Epidemiology of AD

Many estimates have been made about the incidence and prevalence of AD. These estimates have varied widely, specifically relating to the difficulty in defining AD onset. Some studies have only considered the presence of moderate to severe dementia as relevant for indicating AD, whereas others have included mild dementia. The most widely accepted studies have estimated that dementia, mild or greater, affects about 15% of the population over 60 yr of age. Alzheimer's disease (AD) is considered to account for two-thirds of the diagnoses of dementia, thus 10% of the over-60 population. These estimates are the basis for the statement that AD affects about 4 million people in the United States.

Incidence studies have shown clearly that the occurrence of AD increases with age, at a rate very close to doubling of the incidence every 5 yr. Although it has been stated frequently that AD is not part of normal aging, AD is actually related more closely to age than mortality, which doubles in incidence about every 8 yr (*see* Fig. 1). Because the occurrence of AD has such a close relationship to age, it is important to understand the dynamics of AD epidemiology relative to models of the aging process.

The fundamental model of aging is the Gompertz survival function (Sacher, 1977; Strehler, 1977; Hirsch, 1995). The Gompertz curve depends on knowledge of an initial rate of mortality and the doubling time of the rate. This curve applies across the animal kingdom and accounts for more than 99.7% of the variance in mortality after 30 yr of age in the United States for the year 2000 (divide the mortality by age, separated for gender from www.cdc.gov by the population by age from www.census.gov). The slope of the Gompertz survival curve is best explained by a theory that the organism is composed of a number of subsystems that have evolved in a coordinated fashion to manage environmental stresses with optimal energy efficiency (Strehler, 1977).

The incidence rates of AD start much lower than mortality rates but reach 1/1000 by age 62, 1/100 by age 79, and 1/10 by age 94 and approach the mortality rate around age 105. Note that arguments about a healthy survivor effect (Perls et al., 1993) and an occasionally observed decrease in dementia incidence after 90 yr of age actually apply to a very small part of the population and might even represent artifacts (Hirsch, 1994) or noise related to the limits of the genetic and environmental factors that control the life span. Another issue concerns the difference in AD risk related to gender. Although many studies have suggested that females are more susceptible to AD, if there were no gender-related differences in risk, AD would affect about twice as many women just because of the population variations related to age. These calculations specifically indicate that from birth, one-third of all men and two-thirds of all women will contract AD before they die. Thus, a critical issue in AD that has not been addressed is the definition of the Gompertz parameters underlying AD. Gompertzian dynamics presumably have a close relationship to evolution and genetic mechanisms underlying survival and, in the case of AD, to memory and neuroplasticity, which are critical for human survival.

Pathophysiology of AD

The pathophysiology of AD has been studied extensively in the last three decades, since the watershed studies of Blessed et al. (1968) began to clarify the relationship of AD dementia to senile plaques

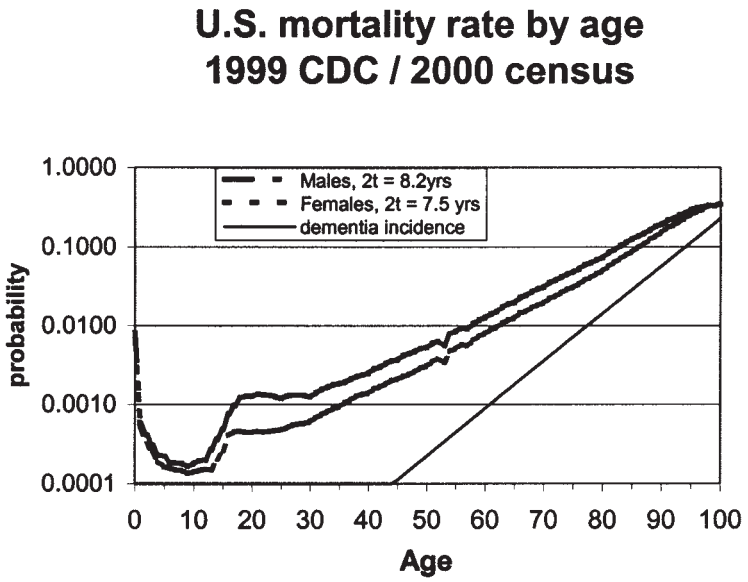

Fig. 1. US mortality rate. Note that a log-linear regression explains over 99.7% of the variance between age 30 and age 100. Mortality rate doubling times (2t) are shown by gender. Dementia incidence is calculated for a population of 4 million affected individuals, with a life expectancy of 10 yr from onset, with a doubling time for the incidence of 5 yr.

(SPs) and neurofibrillary tangles (NFTs). However, these two fundamental pathological hallmarks of AD are not clearly linked. The principle component of SPs is beta-amyloid (Aβ) aggregates, which seem to be closely related to disease causation. Neurofibrillary tangles (NFTs) are mainly composed of hyperphosphorylated tau protein and are closely related to dementia severity. At this point, the best theory to link these AD pathological substrates is to consider that precursors of both substances, the amyloid precursor protein (APP) and the microtubule-associated protein tau, both have important roles in neuroplasticity and memory function. The APP is susceptible to a variety of causative factors, and once the brain has produced a certain excess of Aβ SPs, stress on the tau system leads to progressively more NFTs and more severe dementia. Thus, the pathophysiology suggests that primary AD causation is linked to the processing of the APP.

AD Causation

As AD has become a more clearly defined clinical entity and the pathophysiology has been elucidated, the search has proceeded to causative agents. Although numerous environmental factors have been studied, it appears that AD is predominantly attributable to specific genetic factors. Family studies indicate that first-degree relatives of persons with AD at autopsy have a substantially increased risk of AD relative to controls, and twin studies indicate that the heritability of AD exceeds 70%. A central issue for understanding genetic factors is to explain how the gene operates to cause the disease. Genetic factors in psychiatric disorders appear to affect specific neurophysiological functions, and impaired capacity leads to susceptibility to the disease, that is, there are not specific genes that cause specific mental illnesses.

Gene Effects in AD Causation

There is a variety of ways that genes might cause AD. For example, education, often viewed as an environmental factor protecting against AD, might be a function of earlier genetic influences. More efficient neural storage of information, either biological or learned, could relate to later resistance to AD. Two recent studies (Codemo et al., 2000; Winnock et al., 2002) have shown that individuals who carry one or more apolipoprotein E (*APOE*) ε4 alleles for AD are more likely to stop their education earlier in life. In both of these studies, the effect was evident at a young age, after only a few years of schooling. Also, a genetic factor could influence dietary preferences, thus working through the relationship between the individual and the environment.

There is a variety of specific genetic factors that lead to AD at a relatively young age, under 60 yr old. These genetic factors have been shown to affect the APP. One group of genes affects the sequencing and, hence, the stability, of the APP, whereas another group of genes affects the γ-secretase cleavage of the APP (the presenilin genes). Aberrant genetic factors are also relatively rare; the total number of patients affected is estimated to be less than 5% of all cases. There are many other genes that have been suggested or shown to influence the development of AD at relatively later ages of onset. The genes associated with AD onset at a later age are not related as clearly to the APP, though they might work on the milieu in which the APP is processed, for example, the lipid rafts, which may be controlled by the apolipoprotein E (*APOE*) gene. The gene coding for *APOE* is by far the clearest of the genetic factors that has been associated with relatively later-onset AD (Roses, 1996, 1997), and variations in this gene appear to account for as much as 50% of the population-attributable risk in the United States.

Hypertension and hypercholesterolemia are also common conditions that are associated with AD development, and both are strongly determined by genetic factors. The *APOE* gene is understood most clearly for its role in cholesterol management and thus can itself be associated with the risk for hypertension as well. Because of the many causes of death that affect individuals before the age that dementia usually manifests itself, all such studies are likely to substantially underestimate the genetic factors in AD.

The *APOE* Genotype Might Account for at Least 50% of AD

The clearest genetic factor that has been associated with nonfamilial, or sporadic, AD is the gene that codes for *APOE* (Roses, 1996). In the United States the *APOE* ε4 allele, with a prevalence rate of about 13%, ranging from 10% in East Boston (Evans et al., 1997) to nearly 19% in Cache County, Utah (Breitner et al., 1999; *see* Seshadri et al. [1995], Wilson et al. [1996], Corbo and Scacchi [1999], Liu et al. [1999], and Lehmann et al. [2001] for several worldwide reports), occurs in 22% of the whole population (2% with the ε4/4 genotype and 20% with the ε3/4 genotype) (Table 1). Yet this allele occurs in 60% of AD patients (about 15% with ε4/4 and 40% with ε3/4 and less than 5% with ε2/4). Those individuals with the ε3/3 genotype constitute 60% of the population but only 35% of the cases (Table 2; Saunders et al., 1993; Jarvik et al., 1995; Roses, 1995; Myers et al., 1996; Farrer et al., 1997). On the basis of these broad population studies, if the *APOE* ε4 allele did not exist in the US population, it can be calculated that there would only be half the total number of AD cases. Therefore, the ε4 allele by itself is likely responsible for 50% of the nonfamilial AD cases in this country. Some more focused US studies have found somewhat different results. For example, in Cache County, Utah, a location with an increased frequency of the *APOE* ε4 allele relative to other US locations, this allele appears to account for 70% of the population-attributable risk for AD (Breitner et al., 1999).

The *APOE* genotype has a substantial effect on age-related prevalence of AD, with *APOE* ε4/4 individuals having an estimated 50% chance of AD onset at 68.4 yr of age, *APOE* ε3/4 individuals at 75.5, and *APOE* ε3/3 individuals at 84.3 (Corder et al., 1993). The *APOE* ε4 allele confers its maximal effect on risk before age 70 (Blacker et al., 1997), partly explaining why some studies looking at older populations have not found the full effect of this allele. In the Cache County population, there is a clear relation between the *APOE* genotype and age of risk for developing AD (Breitner et al., 1999).

Relationship to age also appears to be an important factor clinically. In the Lexington (Kentucky) Veterans Affairs Medical Center Memory Disorders Clinic, where 50 probable AD male patients were assessed for age of dementia onset (averaged from estimations derived from chart review, back calculations from MMSE scores, and analysis of SPECT scans), the *APOE* ε4 allele was associated with a significantly younger age of onset (Table 2) (Ashford et al., 2002).

The 2% of the population with the ε4/4 genotype carries 15 times the risk of the 60% of the population that has the ε3/3 genotype and over 20 times the risk of the ε2/3 genotype (*see* Table 1). By the age of 80 yr, 91.3% of patients with the ε4/4 genotype have AD, 47.8% of ε3/4 individuals, and only 20.0% of those without an ε4 allele (Corder et al., 1993). The ε4 allele has been referred to as a susceptibility gene, but no ε4/4 carrier has been shown to reach age 90 without having AD. Alternatively, the ε2 carriers are overly represented among centenarians (Frisoni et al., 2001), and there has still been an inadequate number of ε2/2 carriers examined at late age to define the relationship between this genotype and the classical AD changes at autopsy (Ohm et al., 1999). With consideration of the variation of risk from ε4/4 to ε2/2, more than 75% of the risk of AD might be accounted for by the *APOE* genotype.

Table 1
Frequencies of APOE Genotypes in Control and AD Patients, From Two Multicenter Studies, Predominantly Including the US Population

Genetic type	Sample population		Relative risk	US population > 60		Percent with AD	If all US this type
	Control (%)	AD (%)		General	AD		
			Roses (1995) (from Saunders et al., 1993)				
ε22	1.1	0.0	0.00	503,266	0	0.0	0
ε23	11.0	3.4	0.31	5,032,659	136,364	2.7	1,240,909
ε24	7.7	4.0	0.52	3,522,862	159,091	4.5	2,068,182
ε33	57.1	33.0	0.58	26,169,829	1,318,182	5.0	2,306,818
ε34	20.9	43.2	2.07	9,562,053	1,727,273	18.1	8,272,727
ε44	2.2	16.5	7.50	1,006,532	659,091	65.5	29,988,636
Total no.	91	176		45,797,200	4,000,000	8.7	
no ε4	69.2	36.4	0.53	31,705,754	1,454,545	4.6	2,101,010
an ε4	30.8	63.6	2.07	14,091,446	2,545,455	18.1	8,272,727
			Farrer et al. (1997) (Caucasian, clinic/autopsy studies)				
ε22	0.8	0.2	0.25	366,378	8,000	2.2	1,000,000
ε23	12.7	4.8	0.38	5,816,244	192,000	3.3	1,511,811
ε24	2.6	2.6	1.00	1,190,727	104,000	8.7	4,000,000
ε33	60.9	36.4	0.60	27,890,495	1,456,000	5.2	2,390,805
ε34	21.3	41.4	1.94	9,754,804	1,656,000	17.0	7,774,648
ε44	1.8	14.8	8.22	824,350	592,000	71.8	32,888,889
Total no.	6262	5107		45,842,997	4,008,000	8.7	
no ε4	74.4	41.4	0.56	34,073,117	1,656,000	4.9	2,225,806
an ε4	25.7	58.8	2.29	11,769,880	2,352,000	20.0	9,151,751

These risks are applied to figures from the US 2000 Census (45,797,200 individuals > 60 yr of age) and the estimate that there are 4 million AD cases in the United States. These numbers are used to calculate the percentages of the population with prevalent AD with each *APOE* genotype and with and without an ε4 allele. Also shown are estimates of the number of expected AD cases if all individuals in the United States had this specific genotype. Note that both studies indicate that there would be about half the number of cases in the United States if the APOE ε4 allele did not exist, leading to the conclusion that about half of all cases in this country are attributable specifically to the presence of this allele. Thus, the population-attributable risk for APOE ε4 is about 50% (actually, 0–50%, depending on the stability of the observations). This estimate varies considerably in different countries and for non-Caucasian populations.

A few studies focusing on population incidence of AD have found substantially lower numbers for population-attributable risk associated with the *APOE* ε4 allele, with numbers estimated to be between 7% and 20% of the causative contribution (Evans et al., 1997; Slooter et al., 1998; Warwick Daw et al., 2000; Guo et al., 2001). Several possible factors might explain these low estimates. Incidence studies tend to uncover a relatively small number of cases. Prior elimination of prevalent cases, where there is a large uncertainty in diagnosing the transitional patients, leaves a highly selected population. The uncertainty in early diagnosis will contribute a large random effect to the variation of dementia detection, thus substantially dampening any effect under examination. The population-based studies have selected older populations (over age 65 [Evans et al., 1997], over age 75 [Guo et al., 2001], and mean age of AD onset 82.2 yr [Slooter et al., 1998]), after the age of maximum effect of the *APOE* ε4 allele. These studies have found lower levels of the *APOE* ε4 allele, suggesting that they have examined the resistant survivors. The study that focused on 75 families with AD (Warwick Daw et al., 2000) was likely enriched with rare genetic factors that show higher penetrance than the *APOE* ε4 allele. Consequently, these incidence studies do not disprove the estimations that the *APOE* ε4 allele accounts for approx 50% of the population risk of AD. However, as an individual ages, there will be progressively less effect of specific AD-causing genes and more effects of the environment and nonspecific genes that cause other infirmities or that are protective.

Table 2
Age of Onset and *APOE* Genotype of 50 Probable AD Patients Seen at the Lexington Veterans Affairs Medical Center Over a 2-yr Period

APOE genotype	No.	Mean age of onset (yr)	S.D. (yr)
ε3/3	20	73.6	4.7
ε3/4	20	69.5	6.7
ε4/4	10	68.3	5.6

Age of onset for ε3/3 vs ε4/4, $p < 0.02$; for ε3/3 vs ε3/4, $p < 0.05$).

The present unclarity in the understanding of the impact of the *APOE* genotype points out the importance of age- and gender-specific modeling, which depends on Gompertz formulation. Such analysis requires a large population sample, and the data obtained would include birth date, onset date (to calculate age of onset and check for cohort effects), gender, and *APOE* genotype. The analysis of the Cache County data (Breitner et al., 1999) has not resolved this issue because it uses means and standard deviations, which cannot be transformed into age-specific incidence estimates (*see also* Breitner et al., 2000, erratum; Miech et al., 2002).

An environmental factor that has been associated with AD is dietary cholesterol. A small number of studies have shown highly significant correlations across many countries between dietary fat and cholesterol and the prevalence of AD. However, this finding might be the result of other factors associated with diet. In particular, long-term evolution of genetic factors to support survival in particular dietary and energetic environments might be central to the risk of AD, with imbalances in the *APOE* genotype specifically predisposing to AD and arteriosclerotic disease (Corbo and Scacchi, 1999). Controlled comparisons are needed to elucidate the precise role of diet in AD causation. An interesting conundrum is that dietary habits established early in life could mimic genetic influences, and genetic factors could influence dietary preferences. Recent evidence of a link between cholesterol-lowering drugs and AD prevention (Wolozin et al., 2000; Jick et al., 2000) provides attractive evidence to direct interest to this theory. Of recent great interest is the possible relationship between cholesterol and neuroplasticity (Koudinov and Koudinova, 2001), possibly mediated by an *APOE*–cholesterol complex (Mauch et al., 2001). This interaction could explain how both of these factors might interact to influence the development of AD.

To understand the fundamental role of genetic factors in the environmental context, it is frequently enlightening to take an evolutionary perspective. The evolutionary history of the *APOE* genotype is now being resolved. The *APOE* ε4 allele is the ancestral gene, which existed alone until 300,000 yr ago, at which time the *APOE* ε3 allele appeared. The *APOE* ε2 allele mutated from the ε3 allele about 200,000 yr ago (Fullerton et al., 2000). Although the specific environmental pressures that led to the development of the *APOE* ε3 and ε2 alleles are not known, current worldwide variation of the frequency of these genes suggests that they are beneficial in agrarian societies, particularly those with greater longevity (Corbo and Scacchi, 1999). It is possible that they provided superior cognitive and cardiovascular function to those individuals who lived beyond 60 yr of age and in this way led to the emergence of more complex tribes of early humans. Presumably the human diet changed during this time to include more meat, either because agrarian living conditions made this source of nutrition more abundant or the enlargement of the human brain led to a greater demand for higher caloric food. There is evidence that growth of tooth enamel changed at that time, distinguishing modern humans from earlier hominids (Dean et al., 2001). In the protection of a more organized social environment, elderly individuals could survive, and those elders with retained cognition could provide wisdom to foster the success of the tribe, thereby improving the survival of all members of the tribe. Such wise elders would foster the survival of their own offspring, either as a patriarch that could control his tribe more ably and continue procreating or as a matriarch that could foster the healthier development of her progeny.

In the social context, the specific relation of the *APOE* genotype to cholesterol metabolism might have a complex environmental component still evident in modern times. By observation of the frequencies of

the *APOE* alleles across various populations, there is clearly a geographic variation (Corbo and Scacchi, 1999). The *APOE* ε4 allele is most common in African pygmies (41%), least common in Sardinians (5%), and intermediate in most Western populations (9–19%). The *APOE* ε4 allele has a rate of 8% in India and China, which might account for the lower rate of AD found in India and China compared with Western populations, as this allele seems to have the same association with AD in these countries as it does in Western countries (Liu et al., 1999; Ganguli et al., 2000). The relationship between the *APOE* ε4 allele and AD in Africa has been less clear (Hendrie et al., 2001). This geographical distribution could reflect the disadvantage of the *APOE* ε4 allele in those peoples whose background reflected migration around the world or might indicate that the life-style of Africa is subject to different pressures, possibly including a relatively short life span or different diet composition. The recent theory derived from mitochondrial DNA, that there are three African lines extending back 180,000 yr (Oppenheimer, 2003; Stringer, 2002), whereas non-African lines appear to have branched off about 80,000 yr ago, suggests that there might be numerous other genetic factors involved in AD causation associated with the *APOE* genotype in those individuals who carry the African gene lines. The *APOE* ε3 allele is most common in the Mayans of Central America (91%) and least common in the pygmies (53%). The *APOE* ε2 allele did not exist in aboriginal Americans (*see* Corbo and Scacchi [1999] and Fullerton et al. [2000] for reviews).

Until we know how to modify or prevent the impact of genetic factors associated with AD, we must watch our diets and put safety first in our lives to prevent traumatic brain injury. At this time, genotyping for diagnosis or risk estimation is not accepted standard medical practice, in spite of the important information that it provides. However, many patients and family members are regularly told their *APOE* genotype. This information should be given freely, along with genetic counseling, to those requesting it. Patients and their physicians should use this genetic information to develop strategies to reduce the risk of developing AD, make appropriate plans for the emergence of this disastrous condition, and clarify the diagnosis when the signs first arise. There have been many concerns about the adverse consequences of knowing genotype information. However, dissemination of such knowledge is likely to push research and prevention strategies forward more rapidly.

An important issue in advancing AD research is to improve dementia screening. Appropriate screening techniques would lead to a great increase in the number of AD patients being identified and treated. Screening techniques could advance the recognition of dementia onset substantially. There are several groups currently working to develop better dementia screening tools that can be broadly recommended. A suitable tool could be used as a "sixth vital sign" for routine assessment of individuals over 60 yr of age (Mendiondo et al., 2003). A sampling of screening tools under development can be found at www.medafile.com, including a computerized screening test that is under development. Age-related risk must be considered as a primary factor in determining the positive predictive value of a screening test. By examination of the survival characteristics associated with specific genotypes, we can investigate how a particular genotype influences age of onset of AD. In turn, we might soon be able to use knowledge of the *APOE* genotype to improve the accuracy of screening tests.

References

Arendt T. (2001) Disturbance of neuronal plasticity is a critical pathogenetic event in Alzheimer's disease. *Int. J. Dev. Neurosci.* **19,** 231–245.

Ashford J. W., Kindy M. S., Shih W.-J., Cool C., Aleem B., Cobb L., et al. Clinical onset of Alzheimer's disease (AD) is earlier in patients with an APOE ε4 allele. Annual Meeting, Society for Neuroscience, Orlando, FL, 723.4, 2002.

Ashford J. W. and Jarvik L. (1985) Alzheimer's disease: does neuron plasticity predispose to axonal neurofibrillary degeneration? *N. Engl. J. Med.* **313,** 388–389.

Ashford J. W. and Mortimer J. A. (2002) Non-familial Alzheimer's disease is mainly due to genetic factors. *J. Alzheimer's Dis.* **4,** 169–177.

Ashford J. W., Schmitt F., and Kumar V. (1998a) Diagnosis of Alzheimer's disease, in *Advances in the Diagnosis and Treatment of Alzheimer's Disease,* Kumar, V., and Eisdorfer, C., eds., Springer, New York, pp. 111–151.

Ashford J. W., Mattson M., and Kumar V. (1998b) Neurobiological systems disrupted by Alzheimer's disease and molecular neurobiological theories of vulnerability, in *Advances in the Diagnosis and Treatment of Alzheimer's Disease,* Kumar, V., and Eisdorfer, C., eds., Springer, New York, pp. 53–89.

Ashford J. W., Shan M., Butler S., Rajesekar A., and Schmitt F. (1995) Temporal quantification of Alzheimer's disease severity: 'Time Index Model.' *Dementia* **6,** 269–280.

Ashford J. W., Shih W.- J., Coupal J., Shetty R., Schneider A., Cool C., et al. (2000) Single SPECT measures of cerebral cortical perfusion reflect "Time-Index" estimation

of dementia severity in Alzheimer's disease. *J. Nuclear Med.* **41,** 57–64.
Blacker D., Haines J. L., Rodes L., Terwedow H., Go R. C. P., Harrell, L. E., et al. (1997) ApoE-4 and age at onset of Alzheimer's disease: The NIMH genetics initiative. *Neurology* **48,** 139–147.
Blessed G., Tomlinson B. E., Roth M. (1968) The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br. J. Psychiatry* **114,** 797–811.
Breitner J. C. S., Wyse B. W., Anthony J. C., Welsh-Bohmer K., Steffens D. C., Norton M. C., et al. (1999) APOE-ε4 count predicts age when prevalence of AD increases, then declines: The Cache County Study. *Neurology* **53,** 321–331.
Codemo A., Corti M. C., Mazzetto G., Varotto S., Cortella I., Crepaldi G., and Gabelli C. (2000) Education, APOE status and cognitive impairment in the elderly: an epidemiological study in a rural setting. *Neurobiol. Aging* **21,** S246.
Corbo R. M. and Scacchi R. (1999) Apolipoprotein E (APOE) allele distribution in the world. Is APOE*4 a 'thrify' allele? *Ann. Hum. Genet.* **63,** 301–310.
Corder E. H., Saunders A. M., Strittmatter W. J., Schmechel D. E., Gaskell P. C., Small G. W., et al. (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* **261,** 921–923.
Dean C., Leakey M. G, Reid D., Schrenk F., Schwartz G. T., Stringer C., and Walker A. (2001) Growth processes in teeth distinguish modern humans from *Homo erectus* and earlier hominins. *Nature* **414,** 628–631.
Evans D. A., Beckett L. A., Field T. S., Feng L., Albert M. S., Bennett D. A., et al. (1997) Apolipoprotein E ε4 and incidence of Alzheimer disease in a community population of older persons. *JAMA* **277,** 822–824).
Farrer L. A., Cupples L. A., Haines J. L., Hyman B., Kukull W. A., Mayeux R., et al. (1997) Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: A meta-analysis. *JAMA* **278,** 1349–1356.
Folstein M. F., Folstein S. E., and McCugh P. R. (1975) "Mini-Mental State": A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* **12,** 189–198.
Frisoni G. B., Louhiha J., Geroldi C., and Trabucchi M. (2001) Longevity and the epsilon 2 allele of apolipoprotein E: the Finnish Centenarians Study. *J. Gerontol. A Biol. Sci. Med. Sci.* **56,** M75–M78.
Fullerton S. M., Clark A. G., Weiss K. M., Nickerson D. A., Taylor S. L., Stengard J. H., et al. (2000) Apolipoprotein E variation at the sequence haplotype level: implications for the origin and maintenance of a major human polymorphism. Am. J. Hum. Genet. ***67,*** *881–900.*
Ganguli M., Chandra V., Kamboh I., Johnston J. M., Dodge H. H., Thelma B. K., et al. (2000) Apolipoprotein E polymorphism and Alzheimer's disease: the Indo-US Cross-National Dementia Study, *Arch. Neurol.* **57,** 824–830.
Guo Z., Fratiglioni L., Viitanen M., Lannfelt L., Basun, H., Fastbom J., and Winblad B. (2001) Apolipoprotein E genotypes and the incidence of Alzheimer's disease among persons aged 75 years and older: variation by use of anti-hypertensive medication? *Am. J. Epidemiol.* **153,** 225–231.
Hendrie H. C., Ogunniyi A., Hall K. S., Baiyewu O., Unverzagt F. W., Gureje O., et al. (2001) Incidence of dementia and Alzheimer disease in 2 communities: Yoruba residing in Ibadan, Nigeria, and African Americans residing in Indianapolis, Indiana. *JAMA* **285,** 739–747.
Hirsch H. R. (1994) Can an improved environment cause maximum lifespan to decrease? Comments of lifespan criteria and longitudinal Gompertzian analysis. *Exp. Gerontol.* **29,** 119–137.
Hirsch H. R. (1995) Do intersections of mortality-rate and survival functions have significance? *Exp. Gerontol.* **30,** 147–167.
Jarvik G. P., Wijsman E. M., Kukull W. A., Schellenberg G. D., Yu C., and Larson E. B. (1995) Interactions of apolipoprotein E genotype, total cholesterol level, age, and sex in prediction of Alzheimer's disease: a case-control study. *Neurology* **45,** 1092–1096.
Jick H., Zornbert G. L., Jick S. S., Seshadri S., and Drachman D. A. (2000) Statins and the risk of dementia. *Lancet* **356,** 1627–1631.
Koudinov A. R. and Koudinova N. V. (2001) Essential role for cholesterol in synaptic plasticity and neuronal degeneration. *FASEB J.* **10,** 1858–1869.
Lehmann D. J., Williams J., McBroom J., and Smith A. D. (2001) Using meta-analysis to explain the diversity of results in genetic studies of late-onset Alzheimer's disease and to identify high-risk subgroups. *Neuroscience* **108,** 541–554.
Liu H. C.,. Hong C. J, Wang S. J., Fuh J. L., Wang P. N., Shyu H. Y., and Teng E. L. (1999) ApoE genotype in relation to AD and cholesterol; a study of 2,326 Chinese adults. *Neurology* **53,** 962–966.
Mauch D. H., Nagler K., Schumacher S., Goritz C., Muller E.- C., Otto A., and Pfrieger F. W. (2001) CNS synaptogenesis promoted by glia-derived cholesterol. *Science* **294,** 1354–1357.
Mendiondo M. S., Ashford J. W., Kryscio R. J., Schmitt F. A. (2003) Designing a Brief Alzheimer Screen (BAS). *J. Alzheimers Dis.* **5,** 391–398.
Mesulam M. M. (1999) Neuroplasticity failure in Alzheimer's disease: bridging the gap between plaques and tangles. *Neuron* **24,** 521–529.
Miech R. A., Breitner J. C., Zandi P. P., Khachaturian A. S., Anthony J. C., Mayer L. (2002) Incidence of AD may decline in the early 90s for men, later for women: The Cache County study. *Neurology* **58,** 209–218.
Myers R. H., Schaefer E. J., Wilson P. W. F., D'Agostino R., Ordovas J. M., Espino A., et al. (1996) Apolipoprotein E ε4 association with dementia in a population-based study: the Framingham Study. *Neurology* **46,** 673–677.

Ohm T. G., Scharnagl H., Marz W., and Bohl J. (1999) Apolipoprotein E isoforms and the development of low and high Braak stages of Alzheimer's disease-related lesions. *Acta Neuropathol.* **98,** 273–280.

Oppenheimer S. (2003) The Real Eve: Modern Man's Journey Out of Africa. Carroll and Graf Publishers, New York.

Perls T. T., Morris J. N., Ooi W. L., and Lipsitz L. A. (1993) The relationship between age, gender and cognitive performance in the very old: the effect of selective survival. *J. Am. Geriatr. Soc.* **41,** 1193–1201.

Petersen R. C., Smith G. E., Waring S. C., Ivnik R. J., Tangalos E. G., and Kokmen E. (1999) Mild cognitive impairment, clinical characterization and outcome. *Arch. Neurol.* **56,** 303–308.

Roses A. D. (1995) Apolipoprotein E genotyping in the differential diagnosis, not prediction, of Alzheimer's disease. *Ann. Neurol.* **38,** 6–14.

Roses A. D. (1996) Apolipoprotein E: alleles as risk factors in Alzheimer's disease. *Annu. Rev. Med.* **47,** 387–400.

Roses A. D. (1997) Apolipoprotein E: a gene with complex biological interactions in the aging brain. *Neurobiol Dis.* **4,** 170–85.

Sacher G. A. (1977) Life table modification and life prolongation, in *The Handbook of the Biology of Aging*, Finch, C. E., and Hayflick, L., eds., Van Nostrand Reinhold, New York, pp. 582–638.

Saunders A. M., Strittmatter W. J., Schmechel D., St. George-Hyslop P. H., Pericak-Vance M. A., Joo S. H., et al. (1993) Association of apolipoprotein E allele ε4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* **43,** 1467–1472.

Seshadri S., Drachman D. A., and Lippa C. F. (1995) Apolipoprotein E ε4 allele and the lifetime risk of Alzheimer's disease: what physicians know, and what they should know. *Arch. Neurol.* **52,** 1074–1079.

Shih W.- J., Ashford J. W., Stipp V., Magoun S. L., Coupal J. J., and Gross K. K. (1999) Consecutive brain SPECT surface three-dimensional displays show progression of cerebral cortical abnormalities in Alzheimer's disease. *Clin. Nuclear Med.* **24,** 773–777.

Slooter A. J. C., Cruts M., Kalmijn S., Hofman A., Breteler M. M. B., Van Broeckhoven C., and van Duijn C. M. (1998) Risk estimates of dementia by apolipoprotein E genotypes from a population-based incidence study: the Rotterdam Study. *Arch. Neurol.* **55,** 964–968.

Strehler B. L. (1977) *Time, Cells, and Aging*, Academic Press, New York.

Stringer C. (2002) Modern human origins: progress and prospects. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **357,** 563–579.

Warwick Daw E., Payami H., Nemens E. J., Nochlin D., Bird T. D., Schellenberg G. D., and Wijsman E. M. (2000) The number of trait loci in late-onset Alzheimer disease. *Am. J. Hum. Genet.* **66,** 196–204.

Winnock M., Letenneur L., Jacqmin-Gadda H., Dallongeville J., Amouyel P., and Dartigues J. F. (2002) Longitudinal analysis of the effect of apolipoprotein E ε4 and education on cognitive performance in elderly subjects: the PAQUID study. *J. Neurol. Neurosurg. Psychiatry*. **72,** 794–797.

Wilson P. W. F., Schaefer E. J., Larson M .G., and Ordovas J. M. (1996) Apolipoprotein E alleles and risk of coronary disease. Arterioscler. Thromb. Vasc. Biol. ***16,*** *1250–1255.*

Wolozin B., Kellman W., Ruosseau P., Celesia G. G., and Siegal G. (2000) Decreased prevalence of Alzheimer's disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. *Arch. Neurol.* **57,** 1439–1443.