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Research Article:

Risk of Alzheimer disease is associated with parental age among apolipoprotein E ε4 heterozygotes

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Recent studies have demonstrated an association between apolipoprotein E (APOE) genotype and the risk of Alzheimer disease (AD). There are also several reports suggesting that parental age is a risk factor for AD. We examined APOE genotypes and parental ages in 583 consecutive cases of probable or definite AD ascertained through eight AD specialty clinics, and 1 092 non-demented participants of the Framingham Study who were matched for sex, year of birth and survival age. We found that parents of patients with AD were approximately one year older than parents of controls at the time of birth. This pattern of association was greater among persons having the APOE ε3/ε4 genotype and possibly the APOE ε2/ε3 genotype, but was not evident among subjects with other APOE genotypes. Among APOE ε3/ε4 persons, a 10 year increase in paternal age or maternal age increased the odds of developing AD about 1.6 times. These observations suggest that individuals having both a single copy of ε4 and older parents, have a higher risk for developing AD than persons with only the ε4 risk factor. In contrast, parental age did not appear to influence substantially the risk of AD among ε3 or ε4 homozygotes. There was a trend toward decreased parental age among ε2/ε4 cases compared with ε2/ε4 controls, but a much larger sample of subjects with this genotype is needed to draw firm conclusions. Confounding between maternal and paternal ages did not allow distinction of hypotheses related to male or female reproductive patterns nor diminished the possibility that parental age is a surrogate for an unidentified risk factor. Regardless, the dissimilar patterns of association between parental age and risk of AD across APOE genotype groups suggests that parental age is a modifying rather than a primary risk factor.

Introduction

Epidemiological and molecular evidence suggests there are multiple etiologies for Alzheimer disease (AD). Studies of the incidence and patterns of transmission in families demonstrate that relatives of affected individuals have an increased risk of developing AD compared with members of the general population, but susceptibility is governed by a complex interaction of genes and environmental factors.[1–4] In the past few years, defects in the amyloid precursor protein (APP) gene and two novel genes named presenilin 1 and 2 causing familial (autosomal dominant) early-onset AD (< 65 years) have been identified, but they account for less than 2% of all cases.[5] Apolipoprotein E (ApoE) is a cholesterol binding protein that has three common isoforms encoded by alleles ε2, ε3, and ε4. Association studies have revealed that apolipoprotein E genotype (APOE) is an important susceptibility locus for sporadic and familial late-onset AD in most ethnic and racial groups.[5–7] Risk of AD increases and age at onset decreases as a function of the dose of ε4.[8] APOE may interact with other genetic and environmental factors including head injury,[9] smoking,[10] cholesterol[11] and estrogen[12] in modulating risk.

Parental age at birth has been intensively scrutinized as a potential risk factor for AD. The rationale for these studies is based on the clinical, pathological and neurochemical similarities between AD and Down syndrome and evidence suggesting that the two disorders aggregate in families more frequently than expected.[13–15] Because the risk of Down syndrome rises with increasing maternal age, it was postulated that late maternal age is associated with risk of AD. The findings are inconsistent. Many studies did not show a maternal age effect,[14–24] whereas others reported an association with late maternal age[25–31] and young maternal age.[14]

The influence of paternal age has also been considered. Urakami *et al*[28] found a significant 4.9 year increase in paternal age among a series of 77 patients and 35 controls from Japan. A smaller but highly significant increase in paternal age was reported in a much larger study in Scotland.[24] Three other studies reported a 1.4 year higher paternal age in AD cases, but these differences were not significant perhaps because of small sample size.[16,17,26] In contrast, a significant increase in risk of AD among offspring of younger fathers has been observed.[19,22,32] Paternal age effects were not evident in the data of White *et al*[19] or Hofman *et al*.[21]

The reasons for these inconsistent patterns are unknown but may be related to modifying effects by other genetic and non-genetic factors. In this study, we examined evidence for an interaction between APOE genotype and the parenting ages of mothers and fathers.

Methods

Subjects

Subjects for this study are participants from eight centers in the MIRAGE (Multi-Institutional Research in Alzheimer Genetic Epidemiology) Project. The groups participating in this study are: The Alzheimer's Disease Resource and Referral Center at the Boston University Medical Center (BU); the Geriatric Research Education and Clinical Center, Edith Nourse Rogers Memorial Veterans Hospital, Bedford, MA (Bedford); the Wesley Woods Center at Emory University, Atlanta GA (Emory); the Memory Disorders Unit of the Massachusetts General Hospital (MGH); the Wien Center at Mount Sinai Medical Center in Miami Beach, FL (Miami); the Southern California Alzheimer's Disease Diagnostic and Treatment Center at the Rancho Los Amigos Medical Center, Downey, CA (USC); the Alzheimer Disease Patient Registry at the University of Washington, Seattle, WA (UW); and the Psychiatry Clinic at the Technical University of Munich, Germany (Munich). MIRAGE cases at these centers except UW are consecutively ascertained from a clinic-based population of patients referred for diagnosis of a memory disorder. UW subjects were identified through surveillance of approximately 23 000 participants of a large health maintenance organization. Details regarding patient sampling, diagnostic procedures, and the protocol for collecting family history information are published elsewhere.[2,33] Parental ages were calculated from date of birth information provided by a primary informant on a family history questionnaire. This information was verified by other informants and available medical records.

Of the 1 470 MIRAGE cases from these centers with complete family histories and known parental

ages who met NINCDS/ADRDA criteria for definite or probable AD,[34] DNA was obtained from 106 autopsied subjects and 496 living subjects. These 602 patients (264 men and 338 women) had a mean age at onset of 70.5 ± 10.0 years (range 35–95 years). The groups of subjects with AD enrolled in this study and subjects with AD who were excluded because they could not be genotyped for APOE had similar (39.9% *vs.* 39.0%, respectively) proportions of probands having a positive family history (defined as one or more affected first-degree relatives). However, there were 7.9% more males in the group genotyped for APOE ($p = 0.002$). Also, this group of patients had a mean age at onset of symptoms 1.5 years earlier than those who were unavailable for DNA studies ($p = 0.002$). These differences in gender and age at onset are attributed to the relatively high proportion of MIRAGE cases from the Bedford site who were genotyped for APOE (81% *vs.* 41% at other sites). The Bedford patient series is younger, almost exclusively male and enriched for early-onset cases.

Control data were obtained from 10 333 participants of the Framingham Study.[35] In 1950, 5 209 adult residents of the town of Framingham, Massachusetts were enrolled in a longitudinal study of health. This cohort contained approximately equal numbers of men and women aged 30 to 62 years. The majority were the 4 469 respondents of 6 510 persons selected in a two-thirds stratified sampling of the adult population of the town. Another portion of the cohort, 740 men and women, were volunteers who were the spouses of persons in the sample. Pertinent medical history, psychological, family history, life-style, and demographic data have been systematically collected over biennial examinations since 1950. The remainder of the Framingham Study population comprises children of the original cohort who are participating in a parallel longitudinal study known as the Offspring study. These subjects were enrolled in 1971 and are currently between the ages of 30 and 85 years, with the majority of subjects older than 45 years. Dates of birth for parents of Original Cohort Study subjects were obtained from death certificates.

Dementia has been assessed longitudinally in Framingham participants since 1976 using a neuropsychological test battery and hospital surveillance.[36,37] Subjects with suspected cognitive impairments are called back for a full neurological and neuropsychological examination following a standard protocol.[36,37] Approximately 182 cases were demented (among whom 111 met criteria for probable AD),[38] and these subjects were deemed ineligible as controls. Of the remaining subjects, 1 618 were typed for ApoE isoforms and thus were available for matching with the AD cases. APOE allele frequency data for Framingham Study members has been reported previously.[37,38]

For analytical purposes, the 602 subjects with AD were eligible to be matched with controls based on gender, year of birth, and onset age. Specifically, cases and controls were frequency-matched by year of birth using four categories (1895–1910, 1911–1920, 1921–1930, 1931–1945). Age at onset in the patient was frequency-matched with the censoring age (current age or age at death) in the control subjects using nine age categories (≤ 44, 45–54, 55–59, 60–64, 65–69, 70–74, 74–79, 80–84, ≥ 85 years). Nineteen patients with AD had no matched controls and were subsequently excluded. Up to three controls were matched to each of the remaining 583 cases, yielding 1 508 controls. Demographic characteristics of the final sample of cases and controls are given in Table 1.

Table 1. *Demographic characteristics of patients with AD and controls*

	AD patients		Controls	
Characteristic	N	%	N	%
Gender				
Male	254	43.4	674	44.7
Female	329	56.4	834	55.3
Age group				
≤ 44	1	0.2	3	0.2
45–54	39	6.7	117	7.8
55–59	43	7.4	76	5.0
60–64	77	13.2	183	12.1
65–69	103	17.7	182	12.1
70–74	115	19.7	345	22.9
75–79	132	22.6	385	25.5
80–84	57	9.8	171	11.3
≥ 85	16	2.7	46	3.0
Birth cohort				
1895–1910	137	23.5	404	26.8
1911–1920	276	47.3	805	53.4
1921–1930	128	22.0	209	13.9
1931–1945	42	7.2	90	6.0
Total	583		1508	

APOE genotyping

The APOE assay for the AD cases was performed by polymerase chain reaction (PCR) gene amplification as described previously.[2,33] Methods for the determination of APOE genotypes in the two Framingham Study cohorts were described elsewhere.[38,39]

Analytical procedures

The 10 subjects with the ε2/ε2 genotype (one case and nine controls) were grouped with the ε2/ε3 heterozygotes. Analysis of variance techniques were employed to compute least squares means for parental ages, taking into account the frequency-matching design.[40] Mean parental ages for each APOE genotype group of cases were compared by Duncan multiple range test.[41] The influence of APOE genotype and parental ages on the odds of developing AD was assessed using conditional logistic regression procedures, taking into account the frequency matching design.[42] To accommodate the polychotomous classification of APOE genotype in the regression analysis, four indicator variables were constructed representing the genotype classes ε2/ε2 or ε2/ε3, ε2/ε4, ε3/ε4 and ε4/ε4. These variables took on the value of 1 if the subject had the corresponding genotype, and 0 otherwise. According to this scheme, the ε3/ε3 genotype was considered as the referent. Models were evaluated using the PHREG procedure in SAS.[43] Comparisons of the relative fit of hierarchal models were carried out by computing the difference in the −2 In likelihoods for the models, which follows a χ^2 distribution.

To investigate interaction between parental age and APOE genotype, subjects were classified into 10 discrete groups based on combinations of the five APOE classes and two parental age categories (young or old) using the medians of 31 years and 28 years for paternal age and maternal age, respectively, as the cut-off. Risk ratios for developing AD were calculated for each parental age and APOE genotype group using conditional logistic regression analysis and comparing the odds for old *vs.* young within each APOE group. Standard errors and the covariances among the estimators were used to construct confidence intervals (CI). A formal test of interaction was accomplished by considering a conditional logistic regression model with dummy variables for old parental age and APOE genotypes as well as corresponding interaction terms for these variables. A likelihood ratio test was applied to compare this model with one without the interaction terms.

Results

Table 2 shows that the distribution of APOE genotypes was significantly different between patients with AD and controls ($\chi^2_5 = 375.4, p < 0.0001$). Most of this difference is attributable to the three-fold higher frequency of ε4 (38.8% *vs.* 11.6%; $p < 0.0001$) and a two-fold lower frequency of ε2 (3.3% *vs.* 7.7%; Fisher's Exact test, $p = 7.8 \times 10^{-8}$) among patients. Excluding the persons who have ε4, the frequency of ε2 was still higher among controls than cases (8.6% *vs.* 6.0%; Fisher's Exact test, $p = 0.08$), favoring the

Table 2. *Distribution of APOE genotype in patients with AD and controls*

	AD patients		Controls	
APOE genotype	N	%	N	%
ε2/ε2	1	0.2	9	0.6
ε2/ε3	24	4.1	184	12.2
ε2/ε4	13	2.2	30	2.0
ε3/ε3	192	32.9	985	65.3
ε3/ε4	266	45.6	279	18.5
ε4/ε4	87	14.9	21	1.4
Total	583		1508	

Table 3. *Lease square mean paternal and maternal ages by APOE genotype**

APOE genotype		AD patients N	AD patients Mean	Controls N	Controls Mean	p Value
ε2/ε3	paternal	25	33.3	193	31.9	NS
	maternal		30.1		28.3	NS
ε2/ε4	paternal	13	28.1	30	31.2	NS
	maternal		27.6		29.4	NS
ε3/ε3	paternal	192	31.6	985	31.4	NS
	maternal		28.3		27.8	NS
ε3/ε4	paternal	266	33.3	279	30.8	< 0.0001
	maternal		29.5		28.0	0.007
ε4/ε4	paternal	87	31.6	21	31.4	NS
	maternal		28.0		28.6	NS
All	paternal	583	32.1	1508	31.0	0.004
	maternal		28.9		28.1	< 0.02

*adjusted for gender, age and year of birth.

Table 4. *Odds ratios for developing AD according to paternal age, maternal age, and APOE genotype derived from logistic regression models*

	Paternal age		*Maternal age*		APOE ε2/ε3		APOE ε2/ε4		APOE ε3/ε4		APOE ε4/ε4	
Model	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI
1	1.22	1.06–1.40										
2			1.28	1.08–1.48								
3	1.12	0.93–1.34	1.17	0.94–1.45								
4					0.65	0.42–1.03	2.26	1.14–4.49	4.62	3.65–5.84	20.67	12.42–34.40
5	1.23	1.06–1.42			0.65	0.41–1.02	2.33	1.18–4.63	4.60	3.64–5.83	20.83	12.50–34.73
6			1.26	1.05–1.49	0.65	0.41–1.02	2.23	1.12–4.43	4.56	3.60–5.78	20.76	12.45–34.59
7	1.16	0.96–1.41	1.12	0.88–1.41	0.65	0.41–1.02	2.30	1.15–4.56	4.58	3.62–5.80	20.84	12.50–37.74

*based on 10-year increase, OR = odds ratio, CI = 95% confidence interval.
Odds ratios for APOE genotypes derived assuming a reference odds ratio of 1 for APOE ε3/ε3 genotype

hypothesis that this allele may confer a protective effect.[44]

Mean parental ages for cases and controls according to APOE genotype are presented in Table 3. Among the total group of cases there was suggestive evidence from analysis of variance that paternal ages differed among the APOE genotype groups ($p < 0.06$), but maternal age did not ($p = 0.28$). The ε3/ε4 heterozygotes had a mean paternal age 1.6 years older than the mean for patients with ε3/ε3 ($p < 0.02$) or ε4/ε4 genotypes ($p < 0.07$), and 5.2 years older than the mean for ε2/ε4 patients ($p = 0.01$). Joint evaluation of all patients with AD suggested that ε2/ε4 cases had younger fathers than other cases, although there are small numbers here. Among controls, there were no differences in mean paternal or maternal ages by APOE genotype.

Without adjusting for APOE genotype, AD cases had significantly higher mean paternal ($p = 0.004$) and maternal ($p < 0.02$) ages than controls. To put this finding in perspective, a 10 year increase in paternal age increases the odds of developing AD 1.22 times (Table 4). A nearly identical odds ratio was obtained for maternal age. Comparing cases with controls in the ε3/ε4 group, Table 3 shows that paternal ages of patients with AD were on average 2.5 years older ($p < 0.0001$) and maternal ages were 1.5 years older ($p = 0.007$) than those among controls. Based on a 10 year increase in paternal age, this difference corresponds to odds for subjects in this group developing AD of 1.55 (95% CI = 1.22–1.98; $p = 0.0005$), while a 10 year increase in maternal age yielded an increased odds of 1.41 (95% CI = 1.05–1.63; $p = 0.02$). Cases in the ε2/ε4 group had a mean paternal age that was 3.1 years younger than that of controls, but this result did not attain statistical significance ($p = 0.20$), perhaps because of the small sample size.

In order to evaluate the joint effects of mothers' and fathers' ages and individual APOE genotypes, conditional logistic regression models considering both maternal and paternal ages and APOE genotype as predictors of AD were examined. Table 4 shows that risk of AD increases approximately 1.25 times for each 10 year increase in paternal age or maternal age (models 1 and 2). These observations and the findings that maternal and paternal ages are highly correlated (cases $r^2 = 0.69$, controls $r^2 = 0.66$) and the model comprised of both paternal and maternal ages was significant ($p < 0.006$) when the individual variables were not (model 3) suggest that paternal and maternal ages are confounded. Adding APOE genotype to these models (without considering interaction) does not substantively alter these observations with respect to parental ages (models 4–7).

Table 5 displays the odds ratios for developing AD among older parents *vs.* younger parents within each APOE genotype group. The results suggest that the effect of paternal age is similar among subjects in the APOE ε3/ε3, ε2/ε3 and ε4/ε4 groups with odds ratios varying from 1.2–1.3, although none of these ratios is significantly different from 1.0. Among subjects with the ε3/ε4 genotype, having an older father significantly increases the odds of AD 1.79 times. Small numbers of those with the ε2/ε4 genotype limit our ability to interpret the lower risk of AD among subjects with older fathers.

Table 5. *Odds ratio for developing AD among persons with older parents relative to persons with younger parents by APOE genotype*

APOE genotype	Parents	Young parental age* Cases	Young parental age* Controls	Old parental age# Cases	Old parental age# Controls	Odds Ratio	95% Confidence limits
ε3/ε3	Fathers	93	535	99	450	1.34	0.98–1.84
	Mothers	106	570	86	415	1.13	0.82–1.56
ε2/ε3	Fathers	12	96	13	97	1.16	0.49–2.68
	Mothers	11	113	14	80	2.26	0.95–5.33
ε2/ε4	Fathers	9	18	4	12	0.54	0.12–2.32
	Mothers	6	17	7	13	1.38	0.36–5.25
ε3/ε4	Fathers	120	167	146	112	1.79	1.26–2.54
	Mothers	129	155	147	124	1.62	1.14–2.30
ε4/ε4	Fathers	52	13	35	8	1.26	0.47–3.41
	Mothers	49	15	38	6	2.06	0.72–5.88

*Young paternal age ≤ 31 year, young maternal age ≤ 28 year, #Old paternal age 32 + year, old maternal age 29 + year.

Despite the apparent variable effect of paternal age on risk of AD across APOE genotype groups, formal tests of interaction were not significant. Subjects with older mothers had an increased risk of AD in all APOE groups with odds ratios ranging from 1.1–2.3, however, only the odds ratio among the ε3/ε4 subjects was significant. While we found an effect of parental age, particularly among ε3/ε4 subjects, this effect is overshadowed by the effect of APOE ε4 which confers odds ranging from 2.3–4.6 among heterozygotes to 20 among subjects homozygous for this allele (Table 4).

Discussion

We evaluated the joint effects of APOE genotype and parental ages on risk of AD among 583 rigorously diagnosed and consecutively ascertained patients with AD who were matched to three control subjects on the year of birth, sex and survival age. Our study shows that AD cases have significantly higher paternal and maternal ages than controls. As shown in Table 3, these associations were particularly evident among persons who have the APOE ε3/ε4 genotype. Interestingly, there was a trend toward decreased parental age among ε2/ε4 cases compared with ε2/ε4 controls, but a much larger sample of subjects with this genotype is needed to draw firm conclusions. Multivariate analyses failed to remove the parental age effect (Table 4) and also suggested that maternal and paternal ages are too confounded to resolve whether it is the father's age or the mother's. The parental age effect appeared to be strongest among subjects with the APOE ε3/ε4 genotype (Table 5).

Before seeking a biological explanation for the association between parental age and risk of AD, it is necessary to explore assiduously possible biases in the selection of subjects or artefacts in the results. The patients with AD in this study were ascertained from specialty clinics for memory disorders and may not be representative of all patients with AD. Our sample consisted primarily of white, educated, middle-class subjects. This ascertainment may be related to parenting ages of their mothers and fathers, but in order to distort the association between parental age and APOE genotype, the ascertainment would have to be related to APOE, which is unlikely. The average onset age of persons attending these clinics, particularly those who were able to donate a blood sample, is several years less than the average for affected persons in the general population. However, this difference did not appear to bias our results since parental age effects were evident among both early-onset and late-onset subjects. All patients met criteria for probable or definite AD. The distribution of APOE genotypes in these patients is comparable with those reported for other clinical and epidemiological populations.[7,38,45] This sample is therefore valid for addressing the

question whether risk of AD is influenced separately or by an interaction of parental age and APOE genotype.

There is also a potential concern of recruitment bias since the cases and controls were drawn from distinct populations and may have had different patterns of exposure to non-genetic factors associated with parental age. However, it is unlikely that our results were biased by gender or secular trends in age at parenting because cases and controls were frequency matched for sex and year of birth. Factors pertinent to our analysis including family history of dementia and parental dates of birth are subject to greater recall bias in the AD cases because many of the parents and siblings of controls were interviewed personally. To minimize this possibility, multiple informants were used in data collection for each patient with AD, which has been shown to be very reliable in family studies of AD,[46] and cases lacking dates of birth for both parents were excluded. Moreover, it is difficult to explain how selection or recall bias would account for the variability of parental ages across APOE genotype among AD cases only.

We also wondered whether age at parenthood is a surrogate measure of socioeconomic status. For example, several reports suggest that education level is associated with risk of AD.[47–49] To explore this possibility we included education level and terms for its interaction with parental age and APOE genotype as predictors in the logistic models. Results of these analyses (data not presented) did not change any of our conclusions regarding the association of parental age on risk of AD.

The current findings are at odds with our previous report in which we found an increased risk of AD in persons with young rather than old fathers.[22] However, this association was limited to late-onset patients only. Analysis of this subset of patients in the current data set (without stratifying for APOE genotype) demonstrated a similar but non-significant pattern (AD cases n = 423, least squared mean = 31.9 ± 0.7; controls n = 1 129, least squared mean = 32.5 ± 0.7, $p = 0.5$).

Among other large studies, our results for the total group are consistent with data of Whalley *et al*[24] who found higher paternal ages among 390 population-based patients with AD compared with 780 controls matched for year and place of birth and paternal occupation.[24] However, in that study the effect of maternal age was removed when both father's age and mother's age were entered into the model, whereas in our data the maternal age and paternal age effects could not be disentangled. Our findings, particularly evidence for a variable pattern of association between parental age and risk across APOE genotypes, may explain the lack of consistent findings across studies for parental age as a risk factor for AD. Failure to distinguish APOE genotypes could have masked differences in parental age among patients and controls. For example, our data in Table 3 show no evidence for paternal or maternal age effects among cases and controls with the APOE ε3/ε3 genotype. Lack of a consistent parental age effect in previous studies may also be related to small sample size and selection of controls.

At the present time there are no simple biological explanations for our findings. Mechanisms for a paternal age effect based on Mendelian inheritance or shared environmental factors are unsatisfactory because they don't account for a unique male influence. Moreover, a plausible hypothesis must consider several observations from our study. First, the relative magnitude of the parental age effect on risk of AD is small (10 year odds ratios of about 1.25 in the total group and 1.6 among APOE ε3/ε4 subjects) when compared with that for a single dose (odds ratio of 2.2–4.4) or double dose (odds ratio of 5.1–30.1) of APOE ε4.[5] Second, the parental age effect is significant among ε4 carriers but not among ε3 or ε4 homozygotes. The relatively large impact of ε4 homozygosity may completely overshadow a parental age effect in persons with this genotype. Third, there is suggestive evidence that paternal age has an opposite effect among ε2/ε4 and ε3/ε4 subjects. Fourth, because the maternal age effect is confounded with the paternal age effect, it is entirely possible that paternal age and maternal age are surrogate measures for another yet unidentified risk factor. Taken together, these findings suggest that paternal age and maternal age may be modifying factors rather than primary effects.

How might parental age modify the effect of APOE genotype on risk of AD? The observation of decreased methylation in sperm DNA compared with other tissues of a 3'CpG island in the APOE gene[50] is consistent with a genomic imprinting hypothesis for the paternal age effect in AD,[22] but

direct proof is lacking. The maternal age effect, on the other hand, may be related to increased frequency of mitotic non-disjunction. Several investigators observed aneuploidy of peripheral lymphocytes in patients with AD, especially in familial cases,[51–53] but this finding was unconfirmed in other studies.[54–56] Buckton *et al*[57] suggest that aneuploidy is more likely related to processes concerned with aging than specifically linked to AD. Hormonal changes in older mothers may alter the intrauterine environment and its influence on the developing fetal brain differently according to APOE genotype. The parental age effect might also reflect an age-related increase in germ-line mutations in paternal and perhaps maternal gametes. In order to avoid elimination by selection, however, the effects of such mutations must not be deleterious until after reproductive age. It is well recognized that the frequency of new mutations for many rare Mendelian disorders is associated with increased paternal age, but this relationship is difficult to document for complex genetic diseases like AD without testing specific susceptibility genes. However, despite the highly significant evidence in our study for a parental age effect, it cannot be ruled out that the parental age findings are spurious given the relatively weak effect of this risk factor and the lack of corroborative evidence for a biological hypothesis. Studies of other large samples are needed to confirm our results.

Conclusion

Data in the present study and reports of interaction between APOE genotype and other factors[2,4,9–12,58,59] indicate that, with the exception of unique cases of familial AD caused by rare deterministic mutations,[5] multiple genetic and environmental factors contribute to the development of AD. Joint examination of parental age with these factors may help clarify the role of APOE in the pathogenesis of AD and improve the predictive value of APOE genotype for clinical purposes.

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