

The Apolipoprotein E $\epsilon 4$ Allele Is Associated With Increased Behavioral Disturbance in Alzheimer's Disease

SIR: Abnormal behaviors, such as agitation, aggression, wandering, and hallucinations occur in approximately 25%–50% of Alzheimer's disease (AD) patients,¹ and behavioral disturbance is a common reason for institutionalization in AD.² However, the biological basis for disordered behavior in AD is not understood. The apolipoprotein E $\epsilon 4$ (APOE $\epsilon 4$) allele is a well-established risk factor for AD. Yet it has been difficult to find antemortem phenotypic features that differentiate AD subjects with the $\epsilon 4$ allele from those without it.

We examined the association between two indices of behavioral disturbance and APOE $\epsilon 4$ carrier status in a sample of 77 community-residing subjects with diagnoses of probable AD (24 women, 53 men). Mean age at disease onset was 64.6 years (SE = 0.80); 38 subjects had an age at onset before 65 years. Subjects were rated by their caregivers on the Time-Based Behavioral Disturbance Questionnaire (TBDQ).³ TBDQ score indicates whether, over the previous month, patients showed any of seven disruptive behaviors: combativeness, agitation, wandering, incoherent speech, hallucinations, confusion, and disorientation. To obtain a second measure of be-

havioral disturbance, clinicians evaluated subjects by means of the Alzheimer's Disease Assessment Scale noncognitive subscale (ADAS-noncog),⁴ which contains 10 items relevant to mood, motor, and psychotic disturbance. Cognition was evaluated by means of the Folstein Mini-Mental State Exam (MMSE).⁵ APOE genotyping, using genomic DNA from blood or brain tissue, was performed with standard restriction isotyping methods and yielded the following APOE allele frequencies: $\epsilon 2$ = 0.045; $\epsilon 3$ = 0.552; and the $\epsilon 4$ allele = 0.403.

An analysis of covariance with TBDQ as the dependent variable, MMSE and gender as covariates, and APOE carrier status as the main effect demonstrated significantly greater behavioral disturbance among $\epsilon 4$ carriers ($F_{(1,73)} = 11.0$; $P < 0.002$). A similar analysis, using the ADAS-noncog (available on 65 subjects) as the dependent variable, was also significant ($F_{(1,61)} = 6.0$; $P < 0.02$). There was no significant difference between $\epsilon 4$ carriers and other subjects in mean MMSE score ($t_{(73)} = 0.14$; $P > 0.05$) or in mean age at onset ($t_{(73)} = 0.30$; $P > 0.05$; Table 1).

These results indicate that the APOE $\epsilon 4$ allele is associated with greater behavioral disturbance in AD patients, even when the effects of degree of cognitive impairment and estimated age at disease onset are taken into account. If confirmed, this association could help identify those AD patients more at risk for agitated behavior for early pharmacologic or behavioral management. The biologi-

TABLE 1. Ratings (means \pm standard error) of apolipoprotein E $\epsilon 4$ carriers and noncarriers

Carrier Status	n	TBDQ*	ADAS-noncog**	MMSE	Age at Onset
No	31	21.5 \pm 3.1	5.4 \pm 0.6	13.0 \pm 1.2	64.3 \pm 1.2
Yes	46	34.9 \pm 4.0	8.1 \pm 1.1	13.3 \pm 1.3	64.8 \pm 1.1

Note: TBDQ = Time-Based Behavioral Disturbance Questionnaire; ADAS-noncog = Alzheimer's Disease Assessment Scale—noncognitive subscale; MMSE = Mini-Mental State Exam.

* $P < 0.002$; ** $P < 0.02$.

cal connection between the APOE $\epsilon 4$ allele and behavioral disturbance is unclear. However, neuropathologically, the $\epsilon 4$ allele is associated with increased numbers of plaques containing neurotoxic β -amyloid,⁶ which are found at high density in limbic structures of the medial temporal lobe thought to be important in the regulation of emotion. It is possible that increased injury to these structures in $\epsilon 4$ carriers results in a greater degree of behavioral disturbance.

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Greer M. Murphy, Jr., M.D., Ph.D.
Joy Taylor, Ph.D.
Jared R. Tinklenberg, M.D.
Jerome A. Yesavage, M.D.
Department of Psychiatry and
Behavioral Sciences,
Stanford University School of Medicine,
Stanford, CA 94305

Veterans Affairs
Palo Alto Health Care System
Palo Alto, CA

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