7-1994

The apolipoprotein $\epsilon 4$ allele in Parkinson's disease with and without dementia

K. Marder

Gladys E. Maestre

The University of Texas Rio Grande Valley, gladys.maestre@utrgv.edu

L. Cote

H. Mejia

B. Alfaro

See next page for additional authors

Follow this and additional works at: https://scholarworks.utrgv.edu/som_pub

Part of the [Diseases Commons](#)

Recommended Citation

Marder, K., Maestre, G., Cote, L., Mejia, H., Alfaro, B., Halim, A., Tang, M., Tycko, B., & Mayeux, R. (1994). The apolipoprotein $\epsilon 4$ allele in Parkinson's disease with and without dementia. *Neurology*, 44(7), 1330. <https://doi.org/10.1212/WNL.44.7.1330>

This Article is brought to you for free and open access by the School of Medicine at ScholarWorks @ UTRGV. It has been accepted for inclusion in School of Medicine Publications and Presentations by an authorized administrator of ScholarWorks @ UTRGV. For more information, please contact justin.white@utrgv.edu, william.flores01@utrgv.edu.

Authors

K. Marder, Gladys E. Maestre, L. Cote, H. Mejia, B. Alfaro, A. Halim, M. Tang, B. Tycko, and R. Mayeux

The apolipoprotein $\epsilon 4$ allele in Parkinson's disease with and without dementia

Article abstract—The $\epsilon 4$ isoform of apolipoprotein E (Apo-E) may confer genetic susceptibility for familial and sporadic Alzheimer's disease (AD). Because dementia in AD and Parkinson's disease (PD) share many biologic and clinical features, we determined the Apo-E genotypes for 79 patients with PD, 22 of whom were demented, and for 44 age-matched healthy elderly controls from the same community. We hypothesized that if the dementia was similar to AD, there would be a higher allele frequency of apolipoprotein $\epsilon 4$ (Apo $\epsilon 4$) in demented PD patients compared with nondemented PD patients and controls. The $\epsilon 4$ allele frequency for PD without dementia was 0.132, for PD with dementia, 0.068, and for controls, 0.102. There was no association between Apo $\epsilon 4$ and dementia in the PD patients. We conclude that the biologic basis for dementia in PD may differ from that of AD.

NEUROLOGY 1994;44:1330-1331

K. Marder, MD, MPH; G. Maestre, MD; L. Cote, MD; H. Mejia, BA; B. Alfaro, BA; A. Halim, MPH; M. Tang, PhD; B. Tycko, MD, PhD; and R. Mayeux, MD, MSE

Parkinson's disease (PD) is the third most common cause of dementia in the elderly.¹ The pathogenesis has been attributed to concomitant Alzheimer's disease (AD), cortical and subcortical Lewy bodies, and medial nigral degeneration.² The $\epsilon 4$ isoform of apolipoprotein E (Apo-E) is a genetic risk factor for familial and sporadic AD.³⁻⁵ We determined the Apo-E genotypes for 79 patients with PD, some of whom were demented, and compared these results with those of healthy elderly controls from the same community. We hypothesized that if dementia in PD were due to concomitant AD, the allele frequency of apolipoprotein $\epsilon 4$ (Apo $\epsilon 4$) would be higher in demented PD patients than in nondemented PD patients and controls.

Methods. Subjects. Blood for genomic DNA was obtained from 79 consecutively encountered patients meeting research criteria for PD from a community study of PD in northern Manhattan.⁶ All patients were examined by one of three neurologists (K.M., L.C., R.M.) who have demonstrated excellent interrater reliability on the assessment of extrapyramidal signs.⁷ Patients were considered demented if they met the research criteria established for the diagnosis based on the DSM-III-R criteria and if they or an informant reported functional decline. Blood for genomic DNA was also obtained from 44 healthy elderly nondemented residents from the same community who underwent the same clinical assessments. These individuals were chosen from a pool of 67 by frequency matching for age (within 5 years).

Genomic DNA amplification and restriction isotyping of Apo-E. Apo-E genotypes were determined after isolating DNA from white blood cells and digesting with *HhaI*, using a method modified from the one described by Hixon and Vernier.⁸ All genotypes were determined without knowledge of patient-control status or dementia status.

Data analysis. Allele frequencies for nondemented and demented PD patients and controls were calculated by counting alleles and calculating sample proportions. Frequencies of Apo-E genotypes among the three groups

were compared, using chi-square tests. The groups were also stratified by self-identified ethnic group (white, black, Hispanic) to determine whether there was a higher frequency of the $\epsilon 4$ allele in any ethnic group.

Results. Between March 1, 1993, and October 1, 1993, 79 PD patients (32 men and 47 women) and 44 controls (17 men and 27 women) were evaluated. Demented PD patients ($n = 22$) were significantly older than both nondemented PD patients ($n = 57$) and nondemented healthy elderly controls ($n = 44$). The frequency of whites, blacks, and Hispanics was similar in each group (PD without dementia, PD with dementia, and healthy elderly controls) (table).

Apo $\epsilon 4$ allele frequencies did not significantly differ by age or ethnic group. Apo-E 3/3 was the most

Table. Demographics and apolipoprotein genotype frequencies

	Nondemented PD patients ($n = 57$)	Demented PD patients ($n = 22$)	Controls ($n = 44$)
Age (yr)	71.2	79.2*	72.6
% White	64.9	63.6	60.5
% Black	8.8	9.1	14.0
% Hispanic	26.3	27.3	25.6
Apolipoprotein genotype			
4/4	0.0 (0)	0.0 (0)	0.023 (1)
4/3	0.246 (14)	0.136 (3)	0.163 (7)
4/2	0.018 (1)	0.0 (0)	0.0 (0)
3/3	0.649 (37)	0.818 (18)	0.721 (31)
3/2	0.053 (3)	0.045 (1)	0.091 (4)
2/2	0.035 (2)	0.0 (0)	0.023 (1)

* Significantly different ($p < 0.01$) from nondemented PD patients and controls.
The number of subjects is shown in parentheses.

frequent genotype among nondemented PD patients (0.649), demented PD patients (0.818), and healthy elderly controls (0.721). None of the patients with PD were homozygous for the $\epsilon 4$ allele, while one nondemented control was a homozygote. The frequency of having at least one Apoe4 allele did not significantly differ among the three groups (PD without dementia 0.132, PD with dementia 0.068, and healthy elderly controls 0.102). The frequencies of all possible genotypes are seen in the table. The frequency of Apoe4 did not differ among the three groups when stratified by ethnic group.

Discussion. We found no association between dementia in PD and Apoe4 in demented and nondemented patients with PD. This suggests that the biologic basis for dementia in PD could differ from that of AD.

Although it is unclear whether Apoe4 is a specific risk factor or a susceptibility gene, or is in linkage disequilibrium with the actual risk-causing mutation, the association between Apoe4 and AD appears robust. The frequency of the Apoe4 allele increases in both late-onset familial^{3,9} and sporadic AD.^{4,5} A gene-dose effect occurs; in a study of 42 late-onset families, those with two copies of Apoe4 were 8.1 times as likely and those with one copy of Apoe4 were 2.84 times as likely to have AD than those without Apoe4.⁹ There was also inverse correlation between gene-dose and age of onset of AD in these families.

Risk factors for the development of dementia in PD include late age of onset of motor manifestations, severity of the extrapyramidal syndrome, family history of dementia, and depression.¹⁰ The lack of an association between an increased frequency of the Apoe4 allele and dementia in PD implies that while the dementia of AD and PD share some clinical and biologic features, genetic susceptibility as measured by the Apo-E genotype is distinct in these two disorders. Further clinicopathologic studies will be needed to determine whether Apoe4 can be used to separate those patients whose dementia is due to concomitant AD and those whose dementia is secondary to PD.

From the Gertrude H. Sergievsky Center (Drs. Marder, Cote, Tang, and Mayeux), the Departments of Neurology (Drs. Marder, Cote, Tang, and Mayeux, and H. Mejia and B. Alfaro), Psychiatry (Dr. Mayeux), and Pathology (Drs. Maestre, Tycko, and Mayeux), College of Physicians and Surgeons at Columbia University, New York; the Center for Alzheimer's Disease Research (Drs. Marder, Maestre, Tycko, and Mayeux), New York; and the Division of Epidemiology, Columbia University School of Public Health (Dr. Mayeux and A. Halim), New York, NY.

Support for this project came from the following federal grants: AG10963, AG07232, AG08702, and RR00645, and from the Parkinson's Disease Foundation and the Charles S. Robertson Memorial Gift for Alzheimer's Disease Research from the Banbury Fund.

Received November 22, 1993. Accepted in final form January 20, 1994.

Address correspondence and reprint requests to Dr. K. Marder, G.H. Sergievsky Center, 630 West 168th Street, Columbia University, New York, NY 10032.

References

1. Kokmen E, Chandra V, Schoenberg B. Trends in incidence of dementing illness in Rochester, Minnesota, in three quinquennial periods, 1960-1974. *Neurology* 1988;38:975-980.
2. Rinne JO, Rummukainen J, Paljarvi L, Rinne UK. Dementia in Parkinson's disease is related to neuronal loss in the medial substantia nigra. *Ann Neurol* 1989;26:47-50.
3. Strittmatter WJ, Saunders A, Schmechel D, et al. Apolipoprotein E: high affinity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci U S A* 1993;90:1977-1981.
4. Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of apolipoprotein E allele $\epsilon 4$ with late-onset familial and sporadic Alzheimer's disease. *Neurology* 1993;43:1467-1472.
5. Mayeux R, Stern Y, Ottman R, et al. The apolipoprotein $\epsilon 4$ allele in patients with Alzheimer's disease. *Ann Neurol* 1993;34:752-754.
6. Mayeux R, Denaro J, Hemenegildo N, et al. A population-based investigation of Parkinson's disease with and without dementia; relationship to age and gender. *Arch Neurol* 1992;49:492-497.
7. Richards M, Marder K, Cote L, Mayeux R. Interrater reliability and factor structure of the Unified Parkinson's Rating Scale motor examination [abstract]. *Ann Neurol* 1992;32:250.
8. Hixson J, Vernier D. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *J Lipid Res* 1991;31:545-548.
9. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993;261:921-923.
10. Stern Y, Marder K, Tang M-X, Mayeux R. Antecedent clinical features associated with dementia in Parkinson's disease. *Neurology* 1993;43:1690-1692.