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The Apolipoprotein Epsilon 4 Allele in Parkinson's Disease With and Without Dementia

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The apolipoprotein ϵ4 allele in Parkinson's disease with and without dementia

Article abstract—The ϵ4 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 ϵ4 (Apoϵ4) in demented PD patients compared with nondemented PD patients and controls. The ϵ4 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 Apoϵ4 and dementia in the PD patients. We conclude that the biologic basis for dementia in PD may differ from that of AD.

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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 ϵ4 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 ϵ4 (Apoϵ4) 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 *Hha*I, 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 ϵ4 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).

Apoϵ4 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 ε4 allele, while one nondemented control was a homozygote. The frequency of having at least one Apoε4 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 Apoε4 did not differ among the three groups when stratified by ethnic group.

Discussion. We found no association between dementia in PD and Apoε4 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 Apoε4 is a specific risk factor or a susceptibility gene, or is in linkage dysequilibrium with the actual risk-causing mutation, the association between Apoε4 and AD appears robust. The frequency of the Apoε4 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 Apoε4 were 8.1 times as likely and those with one copy of Apoε4 were 2.84 times as likely to have AD than those without Apoε4.[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 Apoε4 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 Apoε4 can be used to separate those patients whose dementia is due to concomitant AD and those whose dementia is secondary to PD.

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