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APOE genotyping in differential diagnosis of Alzheimer's disease

SIR—The US National Institute on Ageing, and the Alzheimer's Association, (April 20, p 1091)[1] regard apolipoprotein E (*APOE*) genotyping as an adjunctive diagnostic test for Alzheimer's disease, since "patients with Alzheimer's disease are more likely to have an *APOE-ε4* allele than are patients with other forms of dementia". However it is not clear that *APOE-ε4* is more strongly associated with Alzheimer's disease than with dementias of other aetiology. Available data are mainly derived from case series, and may be subject to bias. We present data on *APOE* testing as a differential diagnostic test of Alzheimer's disease in a population-based survey.

In the Rotterdam study (249 demented persons, mean age 83·5 years [SD 7·3], with mild to moderate impairment), Alzheimer's disease, vascular dementia, Parkinson's disease dementia, and other dementias were diagnosed by established criteria.[2] *APOE* genotyping was done as described earlier[3] without knowledge of the diagnosis. *APOE* test characteristics for a diagnosis of Alzheimer's disease were calculated, with patients having another type of dementia as reference, and our diagnostic work-up as the gold standard. The table shows that *APOE-ε4* was equally distributed in Alzheimer's patients and in those with other types of dementia (χ^2 test p=0·35). We found a sensitivity of 0·32 (95% CI 0·26–0·39) and a specificity of 0·61 (95% CI 0·49–0·73) for a diagnosis of Alzheimer's disease based on the presence of at least one *APOE-ε4* allele. For homozygosity testing this was 0·06 (95% CI 0·03–0·10) and 0·95 (95% CI 0·90–1·00), respectively, when heterozygosity was regarded as a negative test result. When one *APOE-ε4* allele was judged to be a non-positive/non-negative result, the sensitivity was 0·09 (95% CI 0·04–0·13) and the specificity 0·93 (95% CI 0·85–1.00), since heterozygotes were excluded from the analysis. The positive predictive value of one *APOE-ε4* allele on Alzheimer's disease (0·69; 95% CI 0·58–0·79) tended to be less than the a priori probability (0·74; 95% CI 0·69–0·80), and was therefore not informative. The probability of Alzheimer's disease in the presence of two *APOE-ε4* alleles slightly increased to 0·80 (95% CI 0·60–1·00). However, the corresponding likelihood ratio of 1·38 (95% CI 0·40–4·74) did not differ significantly from 1, indicating that this test would not be informative either. Our findings were similar for different age categories, for men and women, and were independent of a family history of dementia.

	Alzheimer's disease	Other dementias		
	All (n=185)	All (n=64)	Vascular dementia (n=40)	Parkinson's disease dementia (n=16)
APOE4−E4−	68% (125)	61% (39)	58% (23)	56% (9)
APOE4+E4−	26% (48)	34% (22)	38% (15)	38% (6)
APOE4+E4+	6% (12)	5% (3)	5% (2)	6% (1)

Values are percentages (numbers)

Table: **Presence of *APOE-ε4* in Alzheimer's disease and other dementia types**

Our study suggests that *APOE* genotyping is of little value in distinguishing Alzheimer's patients from other demented patients. A weakness of our study is the lack of neuropathological confirmation. However, in this single-centre, population-based study the antemortem diagnostic work-up was extensive.[2] We found a fairly low *APOE-ε4* frequency in Alzheimer's patients, as did another population-based study.[4] Our study population is quite old, and consequently *APOE-ε4* is less prevalent.[5] However, we also showed that *APOE* genotyping was not informative in younger patients. We conclude that *APOE* genotyping seems to be of limited value in the differential diagnosis of Alzheimer's disease.

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Apolipoprotein E ε4 in bulbar-onset motor neuron disease

SIR—Earlier onset and more rapid disease progression have been correlated with expression of the apolipoprotein E (*APOE*) gene ε4 allele in patients with Alzheimer's disease. Expanding these data to another neurodegenerative disease, Al-Chalabi and colleagues have reported that presentation of sporadic motor neuron disease (MND) as bulbar (brainstem) onset and a trend towards shortened median MND patient survival also may be linked with this ε4 allele.[1] However, unlike findings in Alzheimer's disease, no association with age of onset has been found for ε4 allele expression in either familial (genetically linked) or sporadic MND,[2] nor has pathological association for this allele been identified in Guamanian amyotrophic lateral sclerosis/parkinsonism-dementia complex.[3] We now present data from a North American MND patient population that further limits potential roles for *APOE* ε4 in MND.

Genotyping for *APOE* allelic variation was done between July, 1995, and April, 1996, on 155 patients previously diagnosed with sporadic MND at Baylor College of Medicine, Houston, Texas. Over half of these patients were subsequently assessed for functional disease progression[4] in the Baylor-Muscular Dystrophy Association Amyotrophic Lateral Sclerosis Clinic. After exclusion of patients treated for more than 6 months with insulin-like growth factor 1 (IGF-1) (which slows disease progression[5]), progression rates were assessed for 68 *APOE*-genotyped patients having scores from three or more examinations over at least 6 months.

Total *APOE* genotype and allele frequencies for studied MND patients were not different from reported results for either MND patients or for the general population[2] (see table), and no significant difference in age of MND onset