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Apolipoprotein E4 in the temporal variant of frontotemporal dementia

Although the apolipoprotein E4 (apoE4) allele has consistently been associated with Alzheimer's disease and other types of dementia in many studies,¹ its association with frontotemporal dementia (FTD) is controversial. After our report in 1997 of increased apoE4 allele frequencies in sporadic FTD and its effect on the age at onset,² other studies of cases of FTD with pathological confirmation or tau mutations did not confirm this effect.³⁻⁵ However, recently it has been shown that semantic dementia, the temporal variant of FTD, may be associated with higher frequencies of the apoE4 allele.⁶ Therefore, we have genotyped apoE in our expanded FTD patient population and have assessed whether patients with predominance of temporal atrophy have higher frequencies of the apoE4 allele.

Patients were ascertained through a clinicoepidemiological survey of patients with FTD in The Netherlands.² We identified 111 patients with the diagnosis of probable FTD, established according to the Lund and Manchester criteria. Thirteen of the patients had an autosomal dominant form (defined as at least three affected family members in two generations) of FTD, with tau mutations identified in 10 (P301L, G272V, R406W, and ΔK280), and were excluded from further

analyses. Predominant temporal atrophy, semiquantitatively assessed on CT and/or MRI, was found in 31 (32%) patients, whereas frontal atrophy with or without temporal atrophy was present in 67 (68%) patients. Nine of the 31 patients (29%) with temporal atrophy fulfilled the criteria for semantic dementia, and four patients (13%) showed severe problems in language comprehension, although the diagnosis of semantic dementia could not be definitely established due to incomplete or inconclusive neuropsychological testing. The remaining 18 patients (58%) showed mainly decreased spontaneous speech and word finding difficulties. The clinical diagnosis of FTD was pathologically confirmed in all 17 patients who came to postmortem (five of whom had predominant temporal atrophy). Non-demented control subjects (n=561) were taken from the Rotterdam study.⁷ All patients and controls were genotyped for the apoE allele as described by Slooter *et al.*¹ Both genotype frequencies and apoE4 allele frequencies were calculated for each group and compared with non-demented controls using a χ^2 test.

Six per cent of the 98 patients with sporadic FTD had the apoE4/E4 genotype, compared with 2.3% of non-demented controls (p=0.04). This genotype was present in 9.7% of patients with the temporal variant of FTD (p=0.01) compared with non-demented controls, compared with only 4.5% in patients with frontotemporal atrophy (p=0.5). Genotype frequencies of heterozygote E4 (E4/*) and homozygote E4 (E4/E4) carriers are summarised in table 1. The frequency of the apoE4 allele in all patients with sporadic FTD was 21.9%, compared with 15.3% in the non-demented controls (p=0.02). In patients with temporal atrophy the apoE4 allele frequency was as high as 29.0% (p=0.004), whereas in the patients with frontotemporal atrophy only 18.7% (p=0.3) of alleles was apoE4. No association between ApoE4 and the age at onset, nor the duration of symptoms, was found in the overall group, nor in the subgroups.

Our results show that the apoE4 allele frequency is increased in patients with the temporal variant of FTD compared with non-demented controls. Although a biological hypothesis justifying such an association is still lacking, the effect of the apoE4 allele on the predominance of temporal atrophy compared with frontal atrophy has also been observed in patients with Alzheimer's disease.⁸ To verify the association between the apoE4 allele and the temporal variant of FTD, a large study with pathological confirmation of the clinical diagnosis of FTD is required to exclude admixture of patients with Alzheimer's disease. However, in all 17 patients who were necropsied in our series, including five patients with temporal lobe atrophy, the clinical diagnosis was neuropathologically confirmed. This shows that the clinical criteria according to the Lund and Manchester groups, when combined with neu-

roimaging and psychometric evaluation, are highly accurate. We conclude that the association we previously found between the apoE4 allele and sporadic FTD may be due to a selective increase of this allele in patients with the temporal variant of FTD.

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Transferrin C2 allele, haemochromatosis gene mutations, and risk for Alzheimer's disease

Alzheimer's disease is a neurodegenerative disease characterised pathologically by the presence of neurofibrillary tangles, senile plaques, and selective loss of neurons. Numerous hypotheses have been suggested for the aetiology and pathogenesis of Alzheimer's disease and one that has gained considerable

Table 1 Frequency of apoE genotypes and E4 alleles in different groups

Group	Patients	Genotype†			Alleles		P-value
		E4/E4	E4/*	No E4	%E4		
Non-demented controls	561	2.3%	26.0%	71.7%	15.3	Reference	
Sporadic FTD	98	6.1%	31.6%	62.3%	21.9	0.02	
Temporal lobe atrophy	31	9.7%	38.7%	51.6%	29.0	0.004	
Frontal lobe atrophy	67	4.5%	28.4%	67.1%	18.7	0.3	

†E4/E4, E4 homozygotes; E4/*, E4 heterozygotes; No E4, all other genotypes.