PAPER

The apolipoprotein E ε4 allele selectively increases the risk of frontotemporal lobar degeneration in males

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Objective: To determine whether polymorphic variations in the apolipoprotein E gene (*APOE*) are associated with increased risk of frontotemporal lobar degeneration (FTLD) when mutation in *tau* gene is absent.

Methods: The *APOE* gene was genotyped by polymerase chain reaction from DNA routinely extracted from blood or brain tissues. The *APOE* ε4 allele frequency in 198 patients with FTLD not associated with mutations in *tau* gene was compared with that of a control group of 756 normal individuals drawn from the same geographical region. Analyses were done according to clinical subtype or sex.

Results: The *APOE* ε4 allele frequency (19.4%) was increased (p = 0.01) in FTLD *v* the whole control group (14.1%), while the *APOE* ε2 allele frequency in FTLD (6.5%) was slightly lower than in controls (8.0%) (NS). The *APOE* ε4 allele frequency in men with FTLD (22.3%) was greater (p = 0.002) than in male controls (12.3%); the frequency in women (16.3%) was similar to that in female controls (14.8%) (NS). The *APOE* ε2 allele frequency in men with FTLD was 4.9% while in male controls it was 9.5% (p = 0.06), but there was no difference in women (7.5% *v* 7.9%, NS). Neither the *APOE* ε2 nor *APOE* ε4 allele frequency varied significantly between any of the clinical subtypes.

Conclusions: In FTLD not associated with mutations in *tau* gene, possession of *APOE* ε4 allele in men roughly doubles the chances of developing disease, whereas this has no impact upon disease risk in women.

The ε4 allele of the apolipoprotein E gene (*APOE*) is a risk factor for late onset sporadic and familial Alzheimer's disease.[1] *APOE* ε4 allele frequency may also be increased in frontotemporal lobar degeneration (FTLD),[2–13] though this claim has not generally been substantiated by more recent and usually larger studies.[14–23] Indeed, a recent meta-analysis[19] comparing 364 FTLD patients with 2671 control subjects from many of the above studies found no overall association between *APOE* ε4 allele and FTLD.

FTLD is clinically, pathologically, and genetically heterogeneous, and it remains possible that *APOE* ε4 allele frequency is increased in certain clinical or pathological subgroups which fall under this categorical umbrella. In patients with FTLD associated with mutations in the *tau* gene (FTDP-17), *APOE* ε4 allele frequency is not different from control frequencies.[24 25] However, both Rosso *et al*[13] and Short *et al*[21] have suggested that *APOE* ε4 allele frequency might be increased in patients with semantic dementia (fluent aphasia), compared with those with frontotemporal dementia (FTD) and progressive non-fluent aphasia. In contrast, Pickering-Brown *et al*[16] found *APOE* ε4 allele frequency to be normal in FTD and semantic dementia, but somewhat increased in progressive aphasia. Likewise, several small studies have suggested that *APOE* ε2 allele may be a risk factor for FTLD,[19 26] but again this has not been substantiated.[15 16 18 20 22] Nonetheless, in the aforementioned meta-analysis[19] *APOE* ε2 allele frequency was significantly increased in FTLD compared with controls.

We previously examined *APOE* genotype in 88 patients with FTLD,[16] though only 62 of these patients had been recruited by us, and in only 22 had the diagnosis of FTLD been confirmed at necropsy. We have now extended our own series to 217 patients, with necropsy confirmation in 59 instances. We have been able to double the number of patients with the less common clinical forms of FTLD (that is, semantic dementia and progressive aphasia), in whom previous claims for an increased *APOE* ε2 or ε4 allele frequency had been strongest.[13 16 21]

METHODS

Genomic DNA was extracted from blood or brain tissue (frontal cortex or cerebellum) from a consecutive series of 217 patients (mean (SD) age at onset 59.2 (8.9) years, range 23 to 83) fulfilling current clinical and pathological criteria for FTLD,[27 28] comprising of 115 men (58.8 (8.7) years; 37 to 78) and 102 women (59.7 (9.1) years; 23 to 83). All patients had been recruited between 1987 and 2004 through prospective assessment within the cerebral function unit of University of Manchester by DN, JSS, AR, AV, JT, CJ, and CS. By the time of this study, 62 patients had died and come to necropsy. Pathological confirmation of FTLD was made (by DMAM) in 59 cases, with a diagnosis of cerebrovascular disease (subcortical arteriosclerotic encephalopathy) being ascribed in two women and Alzheimer's disease in one man. These latter three patients were excluded from further study. Furthermore, to avoid potential bias in *APOE* ε4 allele frequencies through Mendelian inheritance and shared allele effects, the 16 FTDP-17 cases (frontotemporal dementia with parkinsonism linked to chromosome 17) in this series with proven mutations in *tau* gene (nine deceased, seven living; 15 with +16 splice site mutation and one with +13 splice site mutation) (see[29 30] and unpublished data) were also excluded, as we have shown by haplotype analysis[31] that all these 15 cases with +16 mutation relate to a common founder and are probably therefore distantly related. Even though the

Abbreviations: FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; MND, motor neurone disease

Table 1 *APOE* genotype and allele frequencies for 198 cases of frontotemporal lobar degeneration, overall and stratified by sex and necropsy confirmation, and 756 control cases, overall and stratified by sex

	APOE genotype						Allele frequency		
Patient group	ε2/ε2	ε2/ε3	ε2/ε4	ε3/ε3	ε3/ε4	ε4/ε4	ε2	ε3	ε4
FTLD									
All patients (198)	1	20	2	111	53	11	6.1	74.5	19.4
Male (103)	0	9	1	55	31	7	4.9	72.3	22.3
Female (95)	1	11	1	56	22	4	7.4	76.3	16.3
Confirmed (50)	1	4	0	30	13	2	6.0	77.0	17.0
Unconfirmed (148)	0	16	2	81	40	9	6.1	73.6	20.3
Controls									
All (756)	2	108	15	445	174	12	8.4	77.5	14.1
Male (227)	2	34	5	136	49	1	9.5	78.2	12.3
Female (529)	0	74	10	309	125	11	7.9	77.2	14.8

Numbers of cases are given in parentheses.
FTLD, frontotemporal lobar degeneration.

16 FTDP-17 cases came from 11 separate families (in three of these families there were multiple members (three in each of two families and two in the third)) and no more than one member in any of the 11 families bore *APOE* ε4 allele, the cases were still excluded. None of the other 198 patients had been shown to bear a mutation within *tau*, nor did any have a family history of similar illness consistent with autosomal dominance.

Hence the final study group comprised of 198 patients constituting 148 currently living and some deceased FTLD patients in whom no necropsy had been done, and 50 necropsy verified patients. In all, 107 patients (54 men and 53 women, mean (SD) age at onset 57.4 (9.2) years, range 23 to 82) were diagnosed clinically with FTD. Of the remainder, 30 patients (19 men, 11 women; mean age at onset 61.6 (8.4) years, range 43 to 78) had frontotemporal dementia and motor neurone disease (FTD+MND), 31 had semantic dementia (12 men, 19 women; onset 60.6 (7.1) years, range 47 to 75), 23 had progressive aphasia (14 men, nine women; onset 64.7 (6.4) years, range 51 to 77), and seven had progressive apraxia (four men, three women; onset 68.0 (9.1) years, range 47 to 65). For all patients, age at onset was determined from an informant (usually the spouse or next of kin) and taken as the age at which relevant symptoms first appeared.

Control data were derived from a cohort of 756 mentally normal people over the age of 50 years resident within the same Greater Manchester region from which the FTLD patients were drawn. Of these, 227 were male and 529 female. A full description of this control cohort has been given previously.[32] All subjects, patients and controls, were white. Given a control *APOE* ε4 allele frequency of 0.14, there was at least 80% power to detect an effect size of 1.7 or greater for the total FTLD cohort and controls, 2.2 or greater for the men with FTLD and male controls, and 2.0 or greater for women with FTLD and female controls.

APOE genotyping was carried out by standard polymerase chain reaction (PCR),[33] as described previously.[15 16]

Statistical analysis

Statistical comparisons of *APOE* allele frequencies were made using the χ^2 test with Yates's correction when 2×2 contingency tables were employed. In accordance with corrections for multiple testing only probability (p) values of less than 0.01 were considered significant. Logistic regression analysis using all cases and controls, with age, sex, *APOE* allele bearer status, and sex versus *APOE* allele interaction as covariables was carried out for both ε2 and ε4 alleles. Statistical analyses were done using SPSS v10.1.

RESULTS

Genotype and allele frequencies compared with controls

APOE allele and genotype frequencies for all 198 patients with clinically diagnosed FTLD and all 756 controls are given in table 1, and also when stratified by sex, presence of necropsy confirmation (see table 1), or clinical subtype (see table 2).

The *APOE* ε4 allele frequency in the 50 deceased FTLD patients where necropsy had been done (17/100 alleles; 17.0%) was not significantly different ($\chi^2 = 0.32$, $p = 0.57$) from that in the 148 currently living and deceased FTLD patients in whom no necropsy had been done (60/296 alleles, 20.3%; table 1). Hence, all 198 patients were subsequently considered as a single group. The *APOE* ε4 allele frequency in the 198 FTLD patients (77/396 alleles, 19.4%) was significantly greater ($\chi^2 = 6.6$; $p = 0.01$; odds ratio (OR) = 1.46 (95% confidence interval (CI), 1.10 to 1.95)) than in the control group as a whole (213/1512 alleles, 14.1%).

The *APOE* ε2 allele frequency also did not differ significantly ($\chi^2 = 0.0$; $p = 1.0$) between the 50 necropsy confirmed

Table 2 *APOE* genotype and allele frequencies for 198 cases of frontotemporal lobar degeneration stratified by clinical subtype

	APOE genotype						Allele frequency		
Clinical subtype	ε2/ε2	ε2/ε3	ε2/ε4	ε3/ε3	ε3/ε4	ε4/ε4	ε2	ε3	ε4
FTD (107)	1	11	1	57	32	5	6.5	73.4	20.1
SD (31)	0	4	0	20	5	2	6.5	79	14.5
PA (23)	0	2	0	13	6	2	4.3	74	21.7
FTD+MND (30)	0	2	1	16	10	1	5	73.8	21.7
PAX (7)	0	1	0	5	0	1	7.1	78.7	14.2

Numbers of cases are given in parentheses.
FTD+MND, frontotemporal dementia and motor neurone disease; FTLD, frontotemporal lobar degeneration; PA, progressive aphasia; PAX, progressive apraxia; SD, semantic dementia.

cases (6/100 alleles, 6.0%) and the 148 living cases (18/296 alleles, 6.1%) (table 1). Again all 198 patients were considered as a single group. In contrast to the *APOE* ϵ4 allele, the *APOE* ϵ2 allele frequency in all 198 patients (24/396 alleles, 6.1%) was lower than that for the control group (127/1512 alleles, 8.4%), though this did not reach statistical significance ($\chi^2 = 2.0$; $p = 0.16$).

Analysis according to sex

The proportions of men to women in the various subgroups (FTD: 55/110 cases, 50%; FTD+MND: 19/30 cases, 63%; semantic dementia: 12/31 cases, 37%; progressive aphasia: 14/23 cases, 61%; progressive apraxia: 4/7 cases, 57%) did not differ significantly ($\chi^2 = 4.7$; $p = 0.32$).

The *APOE* ϵ4 allele frequency was higher in 103 men with FTLD (46/206 alleles, 22.3%) than in 227 male controls (56/454 alleles, 12.3%; $\chi^2 = 9.7$; $p = 0.002$; OR = 2.02 (95% CI, 1.31 to 3.11)). However, as this significant result could have partly reflected the fact that the *APOE* ϵ4 allele frequency was slightly lower in male controls (12.3%) than in female controls (14.8%) ($\chi^2 = 1.65$; $p = 0.22$), and as there is no evidence of a sex difference in other study control groups, we also compared the 103 men with FTLD with all 756 controls (213/1512 alleles, 14.1%). This gave a lower but still significant odds ratio for FTLD ($\chi^2 = 8.6$; $p = 0.003$; OR = 1.73 (95% CI, 1.21 to 2.48)). Among women, there were no significant differences between the 95 cases of FTLD (31/190 alleles, 16.3%) and controls, whether comparing with the 529 female controls (157/1058 alleles, 14.8%; $\chi^2 = 0.17$; $p = 0.58$; OR = 1.12, CI = 0.73–1.70) or with all 756 controls (213/1512 alleles, 14.1%; $\chi^2 = 0.51$; $p = 0.47$; OR = 1.16, CI = 0.76–1.74). The *APOE* ϵ4 allele frequency was marginally higher ($\chi^2 = 1.8$; $p = 0.16$) in men (22.3%) than in women (16.3%) with FTLD (table 1).

Similarly, the *APOE* ϵ2 allele frequency differed very slightly ($\chi^2 = 0.90$; $p = 0.23$) between male controls (43/454 alleles, 9.5%) and female controls (84/1058 alleles, 7.9%). We therefore compared men with FTLD (10/206 alleles, 4.9%) both with male controls ($\chi^2 = 3.5$; $p = 0.06$), and with all controls (127/1512 alleles, 8.4%; $\chi^2 = 2.6$; $p = 0.10$) but in neither instance was a definite significant result obtained, though there was a tendency ($p = 0.06$) for *APOE* ϵ2 allele frequency to be lower in men with FTLD than in male controls. Similarly, women with FTLD (14/190 alleles, 7.4%) did not differ significantly either from female controls (84/1058 alleles, 7.9%; $\chi^2 = 0.02$; $p = 0.88$) or from all controls (127/1512 alleles, 8.4%; $\chi^2 = 0.12$; $p = 0.73$). The *APOE* ϵ2 allele frequency was slightly lower in men with FTLD (4.9%) than in women with FTLD (7.4%), but not significantly so ($\chi^2 = 0.70$; $p = 0.40$) (table 1).

Logistic regression analysis showed no significant interaction between sex and *APOE* ϵ2 or ϵ4 allele, probably because of lack of statistical power (data not shown).

Analysis according to clinical subtype

Although the *APOE* genotype and ϵ2 and ϵ4 allele frequencies were each numerically different across the various FTLD clinical subtypes (table 2), in no instance were such variations statistically significant. There were no significant sex differences in *APOE* ϵ2 or ϵ4 allele frequency between men and women in any of the clinical subgroups (data not shown).

Relation with pathological phenotype

As well as displaying clinical heterogeneity, FTLD is histopathologically diverse. In our previous study,[16] which included only 22 necropsy confirmed FTLD cases, we were unable to demonstrate any relation between possession of *APOE* ϵ4 (or ϵ2) allele and pathological phenotype. We have subsequently reinvestigated any such relation in our present 50 necropsy cases. The *APOE* ϵ4 allele frequency in the 38 patients with microvacuolar-type histology (19.0%) was greater than in the 12 patients with Pick-type histology (8.5%), but not significantly so ($p = 0.18$). By contrast, the *APOE* ϵ2 allele frequency in the 12 patients with Pick-type histology (12.5%) was greater than in the 38 patients with microvacuolar-type histology (4.0%), but again not significantly so ($p = 0.29$).

DISCUSSION

To date, there have been at least 22 studies[2–23] investigating whether the *APOE* ϵ4 allele frequency is increased in FTLD, but no consensus view has emerged. There is similar controversy over the *APOE* ϵ2 allele.[15 16 19 26] Much of this disagreement undoubtedly revolves around the use of (relatively) small studies which have had insufficient power to test the association in what is, compared with Alzheimer's disease, a relatively rare cause of dementia. Moreover, FTLD is clinically and pathologically heterogeneous, and it is possible that an association with the *APOE* ϵ4 allele might exist in one or more of the clinical or pathological subtypes that comprise this condition. The present study is not only by far the largest single series of patients with FTLD so far investigated, but it also includes sizeable numbers of patients with less common clinical forms of the disorder. Indeed, the present cohort is not much smaller than the combined total of 276 other FTLD patients published in studies by research groups other than ourselves and used in the meta-analysis reported by Verpillat *et al*.[19]

In the present study, the *APOE* ϵ4 allele frequency (19.4%) was significantly increased in FTLD compared with mentally normal controls (14.1%), suggesting that this may act as a risk factor for the disorder, but to a much lesser degree than is seen in Alzheimer's disease. Clinical misdiagnosis of FTLD in patients with other neurodegenerative disorders such as Alzheimer's disease—where the bearing of an *APOE* ϵ4 allele is common—has been suggested as a possible explanation for previous reports where *APOE* ϵ4 allele frequency was modestly increased.[2–13] However, sample contamination by misdiagnosed cases of Alzheimer's disease is unlikely to explain our present results for several reasons. First, the *APOE* ϵ4 allele frequency in the pathologically unconfirmed patients was not significantly different from that in the pathologically confirmed patients. Second, of the 217 consecutive clinical cases of FTLD we have investigated, with 62 cases coming to necropsy, there were only three instances in which the diagnosis of FTLD was not pathologically confirmed. Indeed, of these, only one patient had Alzheimer's disease with the *APOE* ϵ3/ϵ4 genotype and two had cerebrovascular disease with the *APOE* ϵ3/ϵ3 genotype. Based on this, our misdiagnosis rate in FTLD using currently accepted criteria[27 28] is low at about 5%, and then usually in favour of forms of dementia other than Alzheimer's disease. Accepting this misdiagnosis rate would mean that there might be about seven cases with actual diagnoses other than FTLD within the 148 currently living or deceased but non-necropsied FTLD patients studied here, though not all these would be likely to have Alzheimer's disease (perhaps two or three), and of those that might have Alzheimer's disease, not all would necessarily have the *APOE* ϵ4 allele. Moreover, it has also been our experience that not one of more than 100 cases of clinically diagnosed Alzheimer's disease we have studied at necropsy has had a pathological diagnosis of FTLD (unpublished observations). Hence, we believe our data truly represent *APOE* ϵ4 allele frequencies in FTLD.

In the present study, men with FTLD were more likely to possess *APOE* ϵ4 allele than women, possession of *APOE* ϵ4 allele roughly doubling their chances of developing FTLD.

Again, misdiagnosis is unlikely to explain this result. There have been no other studies in FTLD where *APOE* ϵ4 allele frequency has been analysed according to sex. The present findings must therefore remain tentative pending replication or support by, for example, a sex specific meta-analysis. Why and how the possession of *APOE* ϵ4 allele might increase the risk of FTLD in men is unclear. Interestingly, possession of *APOE* ϵ4 allele in women increases their risk (relative to men) of developing Alzheimer's disease.[34] Hence any demographic bias in women with *APOE* ϵ4 allele towards the development of Alzheimer's disease might indeed lead to an increased likelihood that men would suffer from FTLD compared with women. However, such a demographic *APOE* ϵ4 allele effect per se should not increase *APOE* ϵ4 allele frequency in men with FTLD, even though the proportion of men affected might be higher. Furthermore, any preferential ''diversion'' of women with ϵ4 allele towards Alzheimer's disease might be expected to lower the *APOE* ϵ4 allele frequency in FTLD relative to control women. Hence, there may be differential biological mechanisms acting in men and women that predispose each towards the two different disorders.

It has been argued that changes in oestrogen signalling pathways, acting through preferential modulation of expression of *APOE* ϵ4 allele (relative to ϵ3 allele) by oestrogen, might selectively increase the risk of Alzheimer's disease in women.[35] In the present study, the *APOE* ϵ2 allele frequency tended to be lower in men with FTLD than in male controls, whereas the frequency of this allele was unchanged in women with FTLD relative to female controls. *APOE* ϵ2 allele frequency in patients with Alzheimer's disease is lower than that in control subjects, suggesting a protective role for this allele.[36 37] Indeed, present data suggest that possession of *APOE* ϵ2 allele in men might halve their chances of developing FTLD. If the ϵ2 allele also plays a protective role in FTLD, the relative lack of this in men with FTLD, in favour of the ϵ4 allele, might facilitate a preferential development of disease. The higher *APOE* ϵ4 and lower *APOE* ϵ2 allele frequencies in men with FTLD seems specific to this disorder, as in a parallel series of 302 patients with Alzheimer's disease assessed in our clinic there were no sex differences in either *APOE* ϵ2 or ϵ4 allele frequencies (unpublished data).

In line with some previous studies,[15 16 24] but in contrast to others,[8 14] we found no association between the possession of the *APOE* ϵ2 or ϵ4 allele, or the *APOE* genotype, and age at onset of disease in any of the clinical groups, or with respect to sex (data not shown here). Such findings are at odds with Alzheimer's disease, where possession of *APOE* ϵ4 allele has been associated with a dose dependent lowering of age at onset.[1] Similarly, and again in contrast to Alzheimer's disease where age at onset is delayed,[1] possession of *APOE* ϵ2 allele or genotype had no effect on age at onset in FTLD, even in men where this allele was underrepresented.

Conclusions

We have shown that *APOE* ϵ4 allele frequency is significantly increased, while the *APOE* ϵ2 allele frequency is reduced, in men with FTLD relative to male controls. While possession of the former allele might act as a risk factor for FTLD in men, the relative lack of *APOE* ϵ2 allele is suggestive of loss of a protective effect which might also play a role in the development of the disease.

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