Apolipoprotein E polymorphism in German patients with frontotemporal degeneration

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Methods: the frequencies of the ε2 and ε4 alleles and the effect of these alleles on the age at onset in 52 patients with frontotemporal degeneration who underwent a thorough diagnostic examination and in 182 cognitively healthy age matched controls were assessed. Genotype comparisons between the groups were performed using multiple logistic regression analysis. Ages at onset according to the apoE genotype were compared by linear regression analysis.

Results: In patients with frontotemporal degeneration apoE ε2 and ε4 allele frequencies were 9.6% each, whereas corresponding frequencies in controls were 9.6% and 9.9%, respectively. There was no significant difference in either ε2 or ε4 allele frequency between the groups. Age at onset was highest in patients with the ε2/ε3 genotype (61.3 years) followed by patients with the ε3/ε3 (58.3 years) and was lowest in patients with the ε3/ε4 genotype (56.4 years) but the differences failed to reach statistical significance.

Conclusion: Allelic variants of the apoE gene do not modulate occurrence or age at onset in this sample of German patients with frontotemporal degeneration.

Methods

The study refers to 52 white patients with frontotemporal degeneration and to 182 cognitively healthy controls which were recruited from a university memory clinic from 1994 to 2001. Within the frontotemporal degeneration group 43 patients had frontotemporal dementia, five had semantic dementia, and four patients had primary progressive aphasia. Most subjects of the control group were cognitively unimpaired spouses of patients from the memory clinic (table 1). Information on age at onset of the disease was obtained from an informant. After informed consent had been obtained blood samples of each patient were taken by venepuncture. The study protocol was approved by the review board of the medical faculty, Technische Universität München. All patients enrolled in this study, including those with frontotemporal dementia, primary progressive aphasia, and semantic dementia, met the consensus criteria for frontotemporal degeneration. All patients underwent a thorough psychiatric, neurological, and neuropsychological evaluation, and there was a second examination in 25 patients by an independent psychiatrist 2 to 3 years later according to the above mentioned criteria to improve diagnostic accuracy. The diagnosis of frontotemporal degeneration was confirmed in all 25 patients. The diagnostic investigation also included an informant interview, a chemistry survey, structural MRI imaging, and functional imaging using either 99mTc HMPAO SPECT or [11C] Pittsburgh Compound B PET imaging.
SPECT or FDG PET. Visual rating of functional images helped to classify patients with frontotemporal degeneration, as every patient with FTD had marked frontal or anterior temporal hypometabolism. Cognitive impairment was assessed using the Cambridge cognitive examination or, from 1998, the Consortium to Establish a Registry of Alzheimer’s Disease Neuropsychological Battery (CERAD-NP) which was completed by the following tests: verbal fluency, Boston naming test, Tower of Hanoi, Stroop colour-word interference, Wisconsin card sorting test, clock drawing, and Rey-Osterrieth figure drawing.

DNA was extracted from blood samples using standard procedures and the apoE genotype was determined as described previously.

Variations in e2 allele or e4 allele frequencies between patients and controls were analysed using the χ² test and logistic regression analysis with age and sex as covariates. The effect of the e2 and e4 gene dosage on age at onset was investigated by Student’s t test and by multiple linear regression analysis.

Due to the low frequency of patients who were homozygous for the e2 allele (n=1) and controls who were homozygous for the e2 (n=1) and e4 (n=1) allele those were collapsed with heterozygous subjects into one group.

RESULTS
Clinical characteristics including age and sex distribution of patients and controls are summarised in table 1. The mean age and sex distribution of both cohorts did not differ significantly. Eighty per cent of patients had onset of the disease before the age of 65.

The frequencies of the ApoE e4 and e2 alleles in the patients were 9.6% each. The corresponding frequencies in controls were 9.9% for the apoE e4 allele and 9.6% for the apoE e2 allele. In patients with frontotemporal degeneration neither the e4 nor the e2 allele frequency differed significantly from the corresponding frequencies in controls even when correcting for age and sex (table 1). It is noteworthy that none of the patients were homozygous for the e4 allele.

In our sample ages at onset were 56.4 (SD 6.7) years in 80 patients and 58.7 (SD 7.6) years in 35 patients homoyzous for the e3 allele, and 61.3 (SD 7.9) years in seven patients collapsed to the e2/e3 genotype. Although ages at onset were lower in patients with the e4 allele and higher in patients with the e2 genotype no significant differences were found in comparison with patients with the e3/e3 genotype.

DISCUSSION
This study of 52 German patients with frontotemporal degeneration showed no differences in apoE e2 or e4 allele frequencies between patients and age matched non-demented controls. Thus our findings are consistent with previous studies using mostly patients characterised by histopathology. The e2 and e4 allele frequencies obtained in this study are within the range of the other studies. By comparison with other studies from northern Germany the e2 allele frequency was a little higher and the e4 allele frequency a little lower in controls than reported. However, the frequencies came close to a Tyrolean study which might be explained by the close geographical vicinity probably indicating a similar genetic background. Our results are at variance with one population based study from The Netherlands which used the Lund and Manchester criteria for clinical diagnosis of frontotemporal degeneration. They reported that the e4 allele frequency (25%) in patients with frontotemporal degeneration was significantly increased compared with controls (15%) which was mainly due to an increase of apoE e4 homozygotes. In our sample, however, no patient with frontotemporal degeneration was homozygous for the apoE e4 allele.

The application of different diagnostic criteria (Lund and Manchester criteria’ versus Consensus criteria’ is unlikely to be the reason for the discrepancy; therefore differences in patient composition are more likely to be responsible. As several studies reported a higher e4 allele frequency in patients with Pick’s disease (although a recent report could not replicate this), a higher proportion of patients with Pick’s disease enclosed may account for the discrepancy. Clinically, it is difficult to distinguish between frontotemporal dementia and Pick’s disease and hence we did not try to differentiate between both entities. The most likely factor—admixture of misdiagnosed patients with Alzheimer’s disease—may account for the higher e4 allele frequencies in patients with frontotemporal degeneration. Although the diagnosis of frontotemporal degeneration was established clinically in this study re-examination in about half of our patients, extensive neuropsychological testing, and functional imaging might have led to an improvement in diagnostic accuracy. Misdiagnosis of patients with Alzheimer’s disease in our patient sample would have resulted in significantly higher apoE e4 allele frequencies compared with the control group, which was not found. In addition, we could not replicate recent findings of a significantly increased apoE e2 allele frequency in patients with frontotemporal degeneration. Although the diagnoses in nine out of 11 patients were confirmed by histopathology the sample size is small and thus may be influenced by spurious effects.

In agreement with two recent findings but by contrast with other reports we were unable to show any effects of the apoE e4 or e2 allele on age at onset. However, due to the low apoE e4 and e2 allele frequencies in our patient cohort, we cannot rule out the possibility that apoE e4 or e2 alleles may influence the age at onset of the disease even without being a significant genetic risk factor.

CONCLUSIONS
Our data suggest that allelic variants of the apoE gene do not modulate occurrence or age at onset of frontotemporal dementia in a sample of German patients. Therefore other not yet identified genes may act as genetic susceptibility factors in frontotemporal degeneration.

| Table 1 Description of the study group, apolipoprotein E genotypes, and allele frequencies |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Subjects (n)                | Age             | Onset           | e4/e4           | e3/e4           | e2/e4           | e4 e3 e2 frequencies % |
| FTD (52)                    | 61.7 (7.7)      | 58.7 (7.6)      | 8               | 2               | 35              | 9.6 80.8 9.6        |
| M (28) F (24)               |                 |                 |                 |                 |                 |                   |
| Controls (182)              | 63.6 (9.3)      |                 | 1               | 31              | 117             | 9.9 80.5 9.6        |
| M (83) F (97)               |                 |                 |                 |                 |                 |                   |

Data are presented as mean (SD).

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