Association Between Tau H2 Haplotype and Age at Onset in Frontotemporal Dementia

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Background: The frontotemporal dementia (FTD) syndromes have been associated with the microtubule-associated tau protein since tau gene mutations have been demonstrated to be the cause of FTD and parkinsonism linked to chromosome 17. In cases of FTD without tau gene mutations, however, it is unclear whether genetic variability in the tau gene is associated with the development or modulation of FTD.

Objective: To determine whether genetic variability in tau and apolipoprotein E (ApoE) modulates and contributes to the development of FTD.

Design and Patients: The distribution of tau gene haplotypes and the ApoE genotype were investigated in 86 patients with well-characterized FTD and 50 control subjects.

Results: No difference in the distribution of the tau H1 and H2 haplotypes between FTD cases and controls was observed, whereas the ApoE ε4 allele was more frequent in FTD cases. The presence of at least 1 tau H2 allele was found to be significantly associated with an earlier age of onset in patients with FTD. The association between the H2 allele and age at onset was not related to family history, clinical presentation, or ApoE genotype.

Conclusion: These findings support a role of tau protein in modulating disease phenotype by influencing the age at onset in these FTD cases.

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The tau gene has been implicated in the development of frontotemporal dementia (FTD) syndromes, as several pathogenic mutations have been found in FTD with parkinsonism linked to chromosome 17.1 Most familial FTD cases have been proved to be clinically, neuropathologically, and genetically heterogeneous and are not associated with tau gene mutations, suggesting that additional genetic, epigenetic, and environmental factors may be implicated in the pathogenesis or modulation of the disease.

Indeed, recent studies have investigated the effect of genetic variability in tau and apolipoprotein E (ApoE) on the development of FTD. Although still controversial,2-5 an association between FTD and the tau H1 haplotype alone or in combination with ApoE ε4 and ε2 alleles6-7 has been suggested.

Apolipoprotein E modulates disease phenotype in Alzheimer disease, in that the presence of the ApoE ε4 allele significantly decreases the age of onset in these patients.8 In FTD, however, no gene has so far been definitely associated with disease modulation, and the role of ApoE ε4 remains controversial.9-12

To determine whether genetic variability in tau and ApoE modulates and contributes to the heterogeneity observed in FTD, we assessed the tau and ApoE genotypes in a cohort of sporadic and familial cases of FTD without tau gene mutations. We found a similar distribution of the H1 and H2 haplotypes between FTD cases and control subjects. However, our results show that the presence of the tau H2 allele leads to a significantly earlier age of onset in FTD. To our knowledge, this is the first report of an influence of the tau H2 haplotype on FTD phenotype.

METHODS

SUBJECTS

Tau exon sequences and ApoE genotype were determined in 86 well-characterized white patients with FTD (hereafter referred to as FTD...
patients or FTD cases (Table). All patients were from East Anglia, an area that covers about 100 miles around Cambridge, England, with more than 2 million inhabitants. The FTD patients underwent assessment in the Early Onset Dementia Clinic at Addenbrookes Hospital, Cambridge, from January 1, 1998, through December 31, 2004. Clinical evaluation of FTD consisted of neurological and neuropsychological testing, which included an interview of family members or caregivers. Structural neuroimaging studies using magnetic resonance imaging were also performed in all cases. All patients fulfilled international consensus criteria for frontotemporal lobar degeneration. In keeping with other studies from the Cambridge group (that included one of us [J.R.H.]), we retained the term frontotemporal dementia as a general superordinate label with a subsequent subdivision into the following 3 major clinical subtypes: behavioral or frontal variant FTD (fvFTD), semantic dementia (SD), and progressive nonfluent aphasia (PNFA).4,13

Patients who were considered to have a positive family history were those who had a first-degree relative with dementia, parkinsonism, or motor neuron disease (amyotrophic lateral sclerosis). To date, 18 of the 86 FTD patients have died. Autopsy was performed in 13 of these patients, and the results revealed the characteristic macroscopic and microscopic neuropathological features of FTD.

For comparison, we also tested the tau and ApoE genes in 50 age- and sex-matched white controls who had no record of neurological or psychiatric symptoms. Controls were recruited from the same geographical area as the patients as part of large population studies on FTD, Alzheimer disease, and multiple sclerosis (performed by J.R.H. and S.J.S.). Patients and controls had a similar range of education. The study was conducted in accordance with local ethical regulations, and an informed consent was obtained from all subjects and caregivers.

DNA EXTRACTION AND TAU SEQUENCE ANALYSIS

Genomic DNA was extracted from blood samples of patients using a commercially available DNA extraction kit (Qiagen Inc, Valencia, Calif). All 13 tau exons and exon-intron boundaries were sequenced in the familial FTD patients. Tau exons 7 and 9 through 13 and exon-intron junctions were analyzed in sporadic FTD cases. Tau exons 7 and 9 were sequenced in controls. DNA amplification with the use of polymerase chain re-

### Table. Demographic and Clinical Characteristics of Patients With FTD Grouped According to Clinical Presentation

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total No. of FTD Cases (N = 86)</th>
<th>hvFTD (n = 51)</th>
<th>SD (n = 27)</th>
<th>PNFA (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>43/43</td>
<td>18/23</td>
<td>22/7</td>
<td>5/3</td>
</tr>
<tr>
<td>Family history</td>
<td>18 (20.9%)</td>
<td>14 (27.4%)</td>
<td>2 (7.4%)</td>
<td>2 (25.0%)</td>
</tr>
<tr>
<td>Frequency of *H1 vs *H2, No. (%)</td>
<td>47 (54.7%) vs 39 (45.3%)</td>
<td>25 (49.0%) vs 26 (51.0%)</td>
<td>16 (59.3%) vs 11 (40.7%)</td>
<td>6 (75.0%) vs 2 (25.0%)</td>
</tr>
<tr>
<td>ApoE e4 genotype, No. (%)</td>
<td>32 (37.2%)</td>
<td>18 (35.3%)</td>
<td>10 (37.0%)</td>
<td>4 (50.0%)</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>57.2 ± 7.7 (86)</td>
<td>55.5 ± 7.8 (51)</td>
<td>59.0 ± 6.9 (27)</td>
<td>58.3 ± 8.4 (8)</td>
</tr>
<tr>
<td>Age at onset with *H1, y</td>
<td>59.2 ± 6.0 (47)</td>
<td>57.7 ± 6.0 (25)</td>
<td>60.4 ± 5.3 (16)</td>
<td>61.3 ± 7.0 (6)</td>
</tr>
<tr>
<td>Age at onset with *H2, y</td>
<td>54.1 ± 8.7 (39)</td>
<td>53.2 ± 8.6 (26)</td>
<td>56.9 ± 8.6 (11)</td>
<td>49.5 ± 6.3 (2)</td>
</tr>
</tbody>
</table>

Abbreviations: ApoE, apolipoprotein E; FTD, frontotemporal dementia; hvFTD, frontal variant FTD; *H1, absence of the H2 allele (H1/H1); *H2, presence of at least 1 H2 allele (H1/H2 or H2/H2); PNFA, progressive nonfluent aphasia; SD, semantic dementia.

*Unless otherwise indicated, data are expressed as mean ± SD (number of cases).
†Significant between *H1 and *H2 carriers (P<.003); otherwise no significant differences were seen between FTD, SD, and PNFA subtypes in the demographic and clinical characteristics.

In total, 86 FTD patients underwent screening. A positive family history was recorded in 18 cases, but no mutations were identified in the tau gene in any of these cases.

Genotype frequencies were compared between cases and controls, but no statistically significant difference was observed, with the following results: H1/H1, 54.7% (n=47) vs 48% (n=24); H1/H2, 40.7% (n=35) vs 48% (n=24); and H2/H2, 4.6% (n=4) vs 4% (n=2) (χ², P = .78). The same was true for the allele frequencies, with both groups showing a similar distribution of H1 and H2 alleles and H1 being the most common allele (χ² test, P = .82). The genotype and allele frequencies were similar to those observed in previous studies.

In this study, *H2 denotes the presence of at least 1 H2 allele, ie, H1/H2 or H2/H2; *H1, the absence of the H2 allele, ie, H1/H1. Results of χ² testing showed that no demographic characteristics, ie, sex or family history of dementia, were associated with *H1 or *H2 (χ² test, P= .75 and P= .53, respectively). However, the presence of *H2

Apoe genotyping

Genetic variation at the ApoE locus was determined by restriction isotyping using polymerase chain reaction amplification and subsequent digestion with restriction enzyme HhaI (New England Biolabs, Ipswich, Mass).

STATISTICAL ANALYSIS

Genotype and allele frequencies between FTD patients and controls were compared by means of the Pearson χ² test. We compared clinical subgroups using the Pearson χ² test, unpaired t test, and analysis of variance (ANOVA). We used the Bonferroni test for post hoc analysis to avoid type II error. We also performed analysis of covariance (ANCOVA) to account for possible confounds. Statistical significance was assumed at P<.05.

RESULTS
form frequency (related significantly with age of onset (Finally, no other demographic or clinical variables cor-
groups (ANOVA, showed an earlier age of onset compared with
allele when adjusting for subgroup diagnosis, and the same
cal characteristics of the subgroups are shown in the Table.

In our study of tau H1 and H2 haplotypes and disease duration in these FTD pa-
patients. A further decrease in the age of onset was ob-
edge, the role of tau haplotypes as a modulator of age of

time, the mechanism by which tau gene polymorphisms
corelation with other disease-modifying fac-
sociated with FTD 

Although the presence of tau gene mutations in FTD with
parkinsonism linked to chromosome 17 has proved the
important association of tau with FTD, the effects of the

gene variability of tau and other genes on the patho-
genesis of familial and sporadic FTD cases without tau
gene mutations remain unclear.

In our study of tau and ApoE genotype frequencies in
86 well-characterized FTD patients, the presence of the
tau H2 allele was associated with a significant decrease
(on average, 5 years) in the age of onset in FTD pa-
patients. A further decrease in the age of onset was ob-
served in patients carrying 2 H2 alleles. To our knowl-
eedge, the role of tau haplotypes as a modulator of age of
onset in FTD has not been previously reported. In our
study, earlier onset in FTD patients carrying the tau H2
allele was seen throughout our data analysis, and it was
independent of clinical presentation (fvFTD, SD, or PNFA)
and familial history.

At present, 18 of the 86 patients have died. Results of
autopsy in 13 of them have confirmed the diagnosis of

For FTD, and the remaining 5 cases have not yet undergone
analysis. Although some of the cases that have not un-
gone autopsy might not have pathological FTD, de-
spite patients' clinical record, the fact that FTD was patho-
logically confirmed so far in all of the cases that underwent
autopsy, together with the imaging study results and the
expertise of the neurology clinic on differential diag-
noses of FTD, makes it reasonable to assume that these
cases represent a largely homogeneous FTD group.

An interesting question that remains to be answered
concerns the relationship between the presence of tau H1
or FTD patients carrying tau H1 and H2 haplotypes.
The remaining 68 patients who are still alive have a disease
duration from presentation that ranges from 1 to 12 years.

No significant association between FTD and the tau H1
or H2 haplotypes was detected, a finding in agreement with
those of previous reports. Furthermore, our results show
an increased frequency of the ApoE ε4 allele in all FTD
subgroups, as also reported by Gustafson et al. However,
like other results, ours do not confirm previous reports of
an association of the ApoE ε4 allele with earlier age of
onset in FTD and do not support a synergistic effect be-
tween tau and the ApoE ε4 allele.

We performed our study in a group of white patients
from the same geographical area, and it will be impor-
tant to extend these studies to a larger cohort of patients
from a wide range of different geographical locations,

Our findings demonstrate a clear association be-
tween the presence of the H2 allele and earlier age at on-
set in FTD and indicate a key role of the tau gene vari-
ability in modulating FTD, even in patients who do not
carry known tau gene mutations.

The mechanism by which tau gene polymorphisms
corelate with the modulation of FTD is currently un-
clear; it could be related to an effect on tau expression
or to an association with other disease-modifying fac-
tors. Indeed, a recent study investigating the effect of tau
haplotypes on tau expression showed that the H1 and H2
alleles have different transcriptional activity in human
cell lines, with H1 being more efficient at driving tau
gene expression.

The fact that the H2 haplotype in our patients was asso-
ciated with earlier onset in all 3 FTD subtypes sug-
gests the existence of common tau-related pathways in-
volved in the development of different clinical FTD
subtypes.

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REFERENCES


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