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.

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, an association between FTD and the tau H1 haplotype alone or in combination with ApoE ε4 and ε2 alleles 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. In FTD, however, no gene has so far been definitely associated with disease modulation, and the role of ApoE ε4 remains controversial.

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 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 (fv FTD), semantic dementia (SD), and progressive nonfluent aphasia (PNFA). Patients who were considered to have a positive family history were those who had at least 1 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 reaction was performed as previously described. The following polymorphisms were used to determine tau H1 and H2 haplotypes in patients and controls: proline 176 in exon 7 and alanine 227 and asparagine 255 in exon 9.

### 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.

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...
(n = 39 carriers) was found to be significantly associated with earlier age at onset compared with *H1 (n = 47 carriers) (mean ± SD age for *H1, 59.2 ± 6.0 years; for *H2, 54.1 ± 8.7 years; t test, P = .003). Further analysis using ANOVA and Bonferroni post hoc tests to compare the 3 groups (H1/H1, H1/H2, and H2/H2) confirmed the effect of the *H2 allele on decreasing the age at onset and revealed that the 4 homozygous H2/H2 cases showed a further decrease of age at onset compared with H1/H1 carriers (mean ± SD age in H2/H2 carriers, 44.5 ± 10.8 years; ANOVA and Bonferroni post hoc analysis, P < .001). Among *H2 carriers, 11 (28.2%) of 39 individuals showed an age at onset younger than 50 years compared with only 3 (6.3%) of 47 of *H1 carriers.

The following numbers of FTD patients were in the 3 clinical subtypes: 51 in fvFTD patients, 27 in SD patients, and 8 in PNFA patients.14,15 Demographic and clinical characteristics of the subgroups are shown in the Table. We performed ANCOVA to evaluate the effect of the *H2 allele when adjusting for subgroup diagnosis, and the same trend for the anticipation of age of onset in *H2 carriers was found (ANCOVA, P < .01). In fact, in any of the 3 clinical subtypes (fvFTD, SD, or PNFA), *H2 carriers showed an earlier age of onset compared with *H1 carriers (ANOVA, P = .02). Mean values are given in the Table.

A significant difference in the distribution of ApoE ε4 isoforms was seen between patients and controls. The ApoE ε4 genotype was significantly more frequent in patients compared with controls (38.6% vs 20.0%; χ² test, P = .03). The 3 FTD subtypes did not differ in ApoE isoform frequency (χ² test, P = .78). The ApoE genotype was not associated with age of onset (t test, mean ± SD age for non–ApoE ε4 carriers vs ApoE ε4 carriers, 56.8 ± 6.4 vs 58.7 ± 7.8 years; P = .24) or family history (χ² test, P = .66). Finally, no other demographic or clinical variables correlated significantly with age of onset (χ² test for sex, P = .92; for family history of dementia, P = .17; for FTD phenotype, P = .14).

**COMMENT**

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 genetic variability of tau and other genes on the pathogenesis 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 patients. A further decrease in the age of onset was observed in patients carrying 2 H2 alleles. To our knowledge, 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 FTD, and the remaining 5 cases have not yet undergone autopsy analysis. Although some of the cases that have not undergone autopsy might not have pathological FTD, despite patients’ clinical record, the fact that FTD was pathologically 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 diagnoses 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 and H2 haplotypes and disease duration in these FTD patients.

Although we have the age at presentation/onset for all of the patients, which corresponds to the date on which they were first referred to and seen by the neurologist or the neuropsychologist, only 18 have died so far and the disease duration (2-14 years) in these 18 is similar between 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. At present, we cannot conclude how long they will have the disease.

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 between 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 important to extend these studies to a larger cohort of patients from a wide range of different geographical locations, population groups, and ethnic origins.

Our findings demonstrate a clear association between the presence of the H2 allele and earlier age at onset in FTD and indicate a key role of the tau gene variability in modulating FTD, even in patients who do not carry known tau gene mutations.

The mechanism by which tau gene polymorphisms contribute to the modulation of FTD is currently unclear; it could be related to an effect on tau expression or to an association with other disease-modifying factors. 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 associated with earlier onset in all 3 FTD subtypes suggests the existence of common tau-related pathways involved in the development of different clinical FTD subtypes.

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REFERENCES


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