

Inheritance of Frontotemporal Dementia

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Background: Previous studies of families with frontotemporal dementia (FTD) support an autosomal dominant inheritance pattern, but most studies have described genetic transmission in individual families specifically selected for the presence of multiple affected individuals.

Objective: To investigate the familial presentation and inheritance of FTD and related disorders among a large group of FTD index cases unselected for family history of dementia.

Design and Setting: We interviewed family members and reviewed medical records and autopsy reports at a university hospital and a university-affiliated hospital to determine the frequency of familial FTD and the most likely mode of inheritance. Characteristic families with the disorder are described, along with the history, clinical findings, and neuroimaging results in affected members of these families.

Patients and Participants: The 42 index cases of FTD had a mean age of onset of 56.1 years (range, 40-69 years). Of these patients, 21 (50%) were women. All but one of the patients were white. Participants included male and female spouses and children of the index cases.

Results: Of 42 FTD cases, 19 (45%) had at least 1 other

family member with an FTD spectrum disorder and were considered familial cases. The majority (17 [89%]) of familial FTD cases showed a pattern consistent with dominant inheritance. If depression is excluded, familial cases decrease from 19 (45%) to 17 (40%), of which 15 (88%) showed a dominant transmission pattern. The initial presentations in the nonindex familial cases varied but most frequently consisted of personality and behavioral changes that preceded cognitive impairment (19 [43%]), followed by psychiatric illness (14 [33%]), dementia without behavioral change (5 [11%]), amyotrophic lateral sclerosis (5 [11%]), and parkinsonism (2 [5%]). Two of the affected nonindex cases had dual presenting diagnoses. The average age of onset was 56.1 years and did not differ significantly between familial and nonfamilial cases. Onset of FTD-related symptoms occurred after the age of 65 years in only 4 (10%) of 42 index cases and 3 (5%) of 60 affected relatives.

Conclusions: Familial FTD is usually inherited in an autosomal dominant pattern. The initial onset is insidious, often consisting of mood and behavioral changes occurring in presenile years that are often erroneously attributed to other nonneurologic causes. Although the precise incidence of FTD in North America is not known, it is one of the most common presenile dementias.

Arch Neurol. 1999;56:817-822

F RONTOTEMPORAL dementia (FTD) is a group of degenerative disorders that overlap in their clinical and neuropathological findings.

At least 25 kindreds have demonstrated heritable FTD disorders.¹ Each disorder was named after its distinguishing characteristic (eg, pallido-ponto-nigral degeneration, familial multiple system tauopathy, familial progressive subcortical gliosis, hereditary dysphasic disinhibition dementia, and disinhibition-dementia-parkinsonism-amyotrophy complex [DDPAC]).¹⁻³ Yet, as a group, these disorders share many clinical and neuropathological findings. Clinical features common throughout the sporadic and inherited FTD range of disorders are presenile onset; behavioral, extrapyramidal, and cognitive (especially frontal executive dysfunction) symptoms; and hypoperfusion in the frontotemporal

region seen on single photon emission computed tomographic (SPECT) scans. However, there is a wide range of presentations that includes depression, bipolar disorder, and alcoholism.^{2,4} Early personality changes and psychiatric disorders often precede frank dementia by many years. Neuropathological findings shared by all FTD disorders are nonspecific and include atrophy in frontotemporal regions, neuronal loss, neuropil vacuolization of superficial cortical layers, and gliosis in gray and white matter.¹

Despite the overlap in characteristics, genetic linkage analysis has demonstrated genetic heterogeneity among FTD kindreds. Half of the 25 kindreds summarized by Foster et al¹ are linked to chromosome 17 and were accordingly renamed FTD and parkinsonism (FTDP) linked to chromosome 17. Linkage to chromosome 17 has been excluded in 4 kindreds, 1 of which was linked to chromosome 3.^{5,6} Frontotempo-

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PATIENTS AND METHODS

PATIENTS

The University of California, Los Angeles (UCLA), Alzheimer's Disease Center, which includes the Memory Disorders and Alzheimer's Disease Clinic and the Harbor-UCLA Neurobehavior Clinic, identified 55 index cases with FTD from 1989 to 1996 on the basis of published criteria.^{9,10} They were not selected on the basis of family history.

Cognitive deficits for each FTD index case were assessed with the following battery: Mini-Mental State Examination (MMSE),¹¹ forward digit span and continuous performance tasks (attention) of the Wechsler Memory Scale,¹² Controlled Oral Word Association Test (FAS), word list generation (verbal fluency),¹³ alternating programs and multiple loops (perseveration), similarities and proverb interpretation (abstract thinking), Rey-Osterreith Complex Figure Test¹⁴ figure copy (visuospatial function), calculations, Boston Naming Test (anomia),¹⁵ objects in array (language comprehension), and verbal repetition tasks.

Diagnostic SPECT scans of the brain and/or autopsy results were obtained for each of the index cases. Frontotemporal dementia was confirmed in 8 autopsy or biopsy cases. Overall, the diagnostic accuracy of patients diagnosed as having FTD through the UCLA Alzheimer's Disease Center has exceeded 90%.¹⁶

Of the 55 index cases, 13 were lost to follow-up owing to death of the affected patient or relocation. Onset ages and ethnicity of the group of patients excluded from the study did not differ significantly from those of the patients whose families were interviewed (data not shown).

PARTICIPANT FAMILIES

A genetic counselor obtained family history through telephone calls to the primary caregiver, usually the patient's spouse. In some cases, contact also was made in person during a regularly scheduled clinic visit. Additional family members were asked to provide collateral history and additional information by telephone. When possible, medical records were obtained to confirm reports of symptoms in family members. To reflect the wide variety of clinical presentations, including common psychiatric disorders in patients with FTD, we defined "positive family history" as the report of any FTD disorders in any first- or second-degree blood relative of the index case, defined as the onset of dementia with or without marked behavioral changes prior to the age of 70 years; psychiatric illness (new onset of reported violence or strange behaviors or diagnosis of depression, bipolar affective disorder, or schizophrenia); amyotrophic lateral sclerosis (ALS); or Parkinson disease.^{1,4,17-20} Because of the high incidence of depression in the general population, we performed separate analyses of the pedigrees with and without depression as a criterion for affected status. We defined onset age as the earliest age at which the presenting symptoms were reported.

Since the number of families was too small for formal segregation analysis, we established the most likely mode of inheritance for each pedigree on the basis of the available family histories. In pedigrees with apparent dominant inheritance, penetrance was calculated by assuming that 50% of the offspring of affected individuals should also be affected if penetrance was complete. For example, if 3 of 6 offspring of an affected parent manifested symptoms prior to the age of 60 years, the calculated penetrance at the age of 60 years would be 100%.

ral dementia is also neuropathologically heterogeneous. Some families with FTDP linked to chromosome 17 have tau-immunoreactive inclusions, whereas others do not.¹ Cases of FTDP linked to chromosome 17 vary widely in terms of regional pathological characteristics, as evidenced by the juxtaposition of DDPAC, progressive subcortical gliosis, and pallido-ponto-nigral degeneration.¹ Additionally, some familial FTD cases have inclusions that resemble Pick bodies,^{7,8} and some reveal a markedly asymmetrical, left- or right-dominant distribution of the classic neuronal loss, neuropil vacuolization, and gliosis.

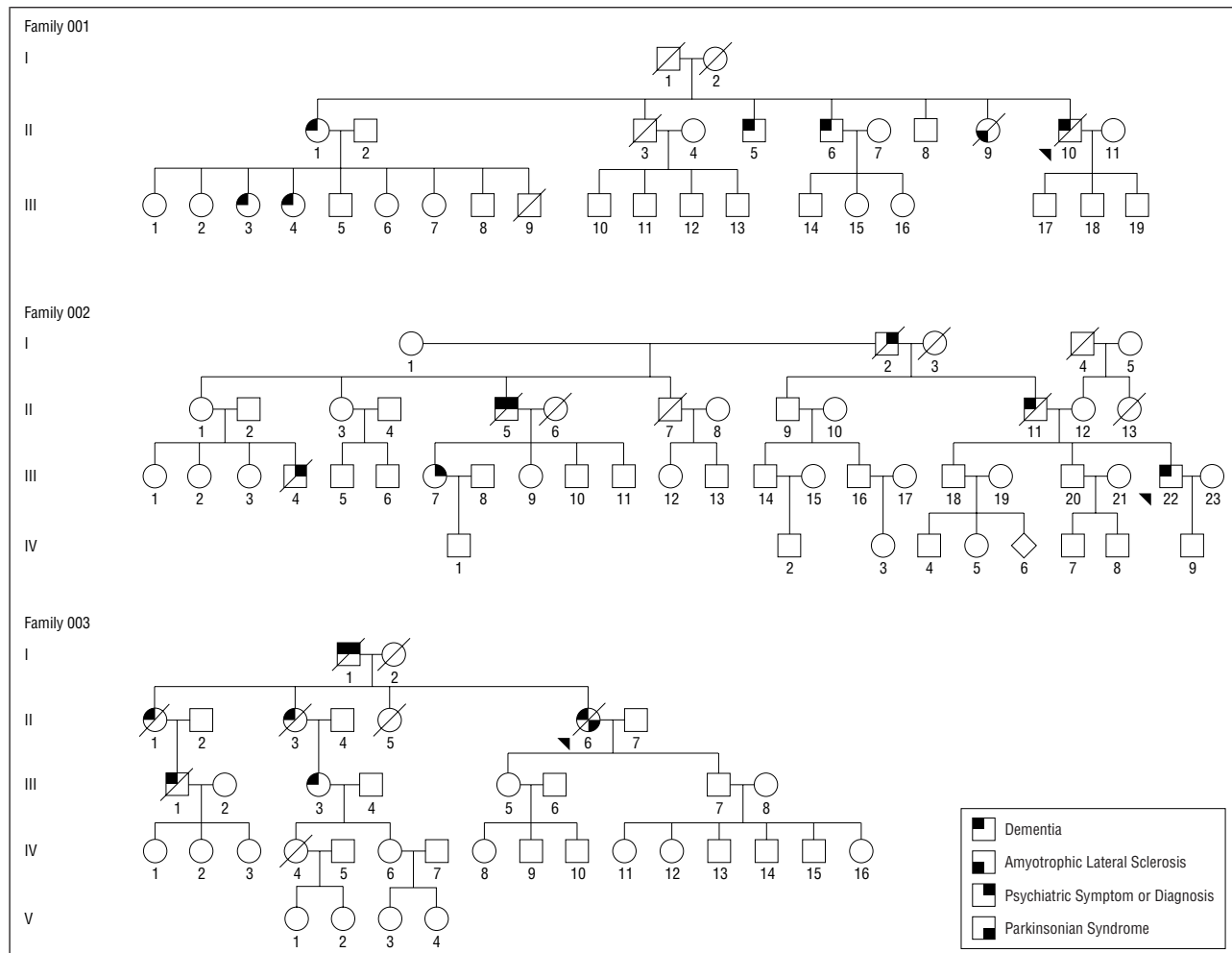
Determination of the familial nature and inheritance patterns of such divergent FTD disorders requires analysis of a large collection of FTD pedigrees. Most previous studies¹⁻⁵ have included only selected families with FTD. We have analyzed the family history of dementia and pedigree structure in 42 unselected index cases of FTD to more reliably establish the extent to which FTD is inherited.

RESULTS

Of the 42 index cases for whom information was obtained, 19 had affected first- or second-degree relatives. Of the 19 pedigrees, 17 (89%) with a positive family history had affected relatives in 2 or more suc-

cessive generations, consistent with autosomal dominant inheritance. Transmission of the assumed autosomal dominant trait was observed in male-to-male, male-to-female, female-to-female, and female-to-male pairs. The 23 index cases without any affected family members were labeled sporadic, although a recessive mode of inheritance was also possible. The 2 pedigrees with affected second-degree relatives and questionably affected first-degree relatives were designated as showing an "uncertain inheritance pattern."

Considering only those with a positive family history, a total of 194 first-degree descendants of affected individuals were potentially at risk for FTD. Under the assumption of full penetrance of a dominant trait, one would expect 97 of the at-risk offspring to be affected. A total of 60 affected offspring were identified from this cohort (see the "Patients and Methods" section), which represents a 62% overall penetrance. As expected, penetrance increased with increasing age. Penetrance (95% confidence interval) averaged across all 17 pedigrees was 28% (14%-42%) at the age of 40 years, 52% (34%-70%) at 50 years, 75% (60%-90%) at 60 years, 88% (88%-89%) at 70 years, and 100% at 80 years. Symptom onset after the age of 65 years in offspring of affected individuals was unusual; we observed it in only 4 individuals from 2 (12%) of the 17 families. Conversely, affected rela-



Families 001 through 003 illustrate transmission consistent with autosomal dominant inheritance. Arrowheads indicate index cases.

tives in 15 families (88%) with presumed autosomal dominant inheritance of FTD had onset of symptoms prior to the age of 65 years.

The average age of onset in index cases was 56.1 years. The mean age of onset did not differ significantly on the basis of sex (men, 55.5 years [range, 40-69 years]; women, 56.9 years [range, 30-69 years]); presence of family history (positive family history, 53.1 years [range, 40-67 years]; negative family history, 58.7 years [range, 42-69 years]); sex of the parent transmitting the disease (affected father, 52.5 years [range, 40-67 years]; affected mother, 54.3 years [range, 30-62 years]); or pattern of inheritance (presumed autosomal dominant, 54.1 years [range, 40-67 years]; sporadic, 58.3 years [range, 42-69 years]). In 4 index cases, the age of onset of the disease was older than 65 years: in 2, the mode of inheritance was apparently autosomal dominant, and in the other 2, it was sporadic or recessive.

In addition to the index cases, there were 43 affected first-degree relatives within the 17 families with presumed dominant inheritance. These affected first-degree relatives manifested the following clinical conditions: dementia with marked behavioral change (19 [44%]); psychiatric illness (14 [33%]); dementia without behavioral change (5 [12%]); ALS (5 [12%]); and par-

kinsonian symptoms (2 [5%]). Of the affected 43, 2 had dual presenting diagnoses. Thus, a total of 45 presentations are considered. One affected individual had dementia and schizoaffective disorder; another affected individual had both ALS and Parkinson disease. No individuals who were not index cases with ALS or parkinsonism were known to have dementia at the time of the interviews.

The elimination of affected relatives with only depression changed the likely mode of inheritance in 2 of the 17 families from presumed autosomal dominant to sporadic, reducing the number of families with an affected first-degree relative from 17 (45%) to 15 (40%). This only changed the percentage of familial cases showing a dominant transmission pattern from 17 (89%) of 19 to 15 (88%) of 17 but reduced the absolute number of familial cases to 17 (40%) of 42.

To illustrate the varied clinical presentations, 3 representative pedigrees with presumed autosomal dominant inheritance are described briefly below (Figure).

In the index case in family 001, FTD initially manifested at the age of 61 years with a change in his sleep/wake cycle and several misperceptions, including the illusion that his mirror image was actually that of his brother. Family members noted an unusual change in his

ability to identify familiar individuals by voice on the telephone. When callers identified themselves, he would contest their identities, and he frequently disconnected relatives who tried to maintain the telephone conversation. Nevertheless, the patient was able to identify other sounds, such as music. Mental status testing 2 years into the course of illness revealed an MMSE score of 19/30, poor insight and attention, poor language comprehension and moderate anomia, decreased verbal fluency, perseveration, poor abstract thinking, apraxia, very mild visuospatial impairment, and intact calculations. Magnetic resonance images of the brain showed evidence of frontal atrophy. Hexylmethylpropylene amineoxine SPECT scans showed hypoperfusion in the bifrontal region with posterior sparing. Three years into his illness, he was more bland and apathetic, experienced incontinence of stool and urine, used highly repetitive speech, and gorged on food. Neuropathological examination confirmed FTD.

Of the index case's 6 siblings, 4 have been diagnosed as having FTD or ALS. The youngest of the index case's sibblingship (II:9) died of ALS at the age of 43 years. At the age of 65 years, individual II:6 has difficulty recognizing telephone callers. On mental status testing, he had a slightly blunted affect, a tendency to giggle with mild euphoria, a poor attention span (forward digit span), slightly diminished verbal fluency (Controlled Oral Word Association Test [FAS]), and an MMSE score of 29/30. Brain SPECT scans revealed hypoperfusion in the anterior bitemporal region, which was more pronounced on the left side, with hippocampal sparing. A third sibling (II:5) had onset of dementia at the age of 62 years and a SPECT scan showed bilateral hypoperfusion in the perisylvian region. Individual II:1 was diagnosed as having FTD with onset at the age of 60 years. The SPECT scan showed hypoperfusion predominantly in the left temporal region. Of her daughters, 2 (III:3 and III:4) had difficulty identifying telephone callers, but they showed no other cognitive deficits. The left-sided asymmetrical involvement found in other affected relatives was also observed on their SPECT scans.

The index case (III:22) in family 002 had worked successfully as an advertising executive, writer, and real estate developer before he began to abuse alcohol at the age of 50 years. He became an accident-prone driver at the age of 51 years. Over the next 2 years his attention span decreased; his behavior changed from assertive to passive; he made inappropriate sexual comments to women; masturbated in public; tended to lie and cheat at board games; preferred sweets and meat, causing a 6.75-kg weight gain; watched television compulsively; and made impulsive purchases over the telephone. He also manifested a form of environmental dependence by mirroring his wife's behaviors (eg, ordering the same meal at a restaurant or simulating her dress). On examination 2 years into the illness (at age 53 years), the patient was cooperative but restless and perseverative, scored 26/30 on MMSE, and had mildly impaired attention and verbal recall. Magnetic resonance images of the brain showed frontal atrophy. Xenon Xe 133 SPECT scans showed hypoperfusion in the bifrontal and right temporal regions. Four years later, the patient continued to gain weight and developed behavior changes, such as staring and inap-

propriately following people, urinary incontinence, and stereotyped speech, with an MMSE score of 23/30. Five years into his illness, the patient developed bruxism and mutism. The index case's paternal grandfather (I:2) was known as a chronically eccentric, cantankerous, and disinhibited man with a habit of chewing on young girls' ears. The index case's father (II:11) had early-onset dementia; a paternal uncle (II:5) suddenly switched careers before the onset of marked apathy in his 40s. Individuals III:4 and III:7 have mood disorders.

In family 003, the index case's grandfather (I:1) committed suicide by setting himself on fire after 7 years' deterioration in financial management skills. Individual II:1 developed a disinhibited dementia in her 60s. In her son (III:1), the onset of dementia and behavioral changes occurred in his 40s. The index case's mother (II:3) experienced incontinence and dementia in her 60s. The index case (III:3) had progressive right temporal degeneration, manifested at first by numerous extramarital affairs, physical violence toward her husband, an obsession with cosmetic surgery, and depression. Later, she experienced disorientation and forgetfulness that developed into severe dementia with left hemineglect, although her language abilities remained relatively intact. Individual II:6 exhibited behavior changes in her 40s, losing interest in social interactions; she became more clearly demented in the last 5 years of life and died in her 60s.

COMMENT

This is the first pedigree analysis in North America designed to establish the familial nature of FTD, a heterogeneous group of early-onset dementias characterized by marked behavioral changes. Of the unselected FTD index cases referred to the UCLA Alzheimer's Disease Center, 40% to 45% had a positive family history. Although the number of families in our study was too small for formal segregation analysis, 17 (89%) of the 19 pedigrees with a positive family history showed inheritance patterns consistent with dominant transmission, confirming previously reported familial cases in which FTD is typically inherited as an autosomal dominant trait.^{1,2,4,20-22} The high risk to first-degree relatives of FTD index cases with a family history has significant genetic counseling implications. Once the mutational basis of FTD is known, genetic testing can be used to diagnose younger patients with the disease or for gene carrier status. Early diagnosis through genetic testing may be most helpful in predictive testing and in diagnosing affected relatives with uncertain phenotypes, such as alcoholism or mood disorders, in addition to distinguishing this condition from Alzheimer disease.

These findings are consistent with recent data from a comprehensive epidemiological population survey in the Netherlands in which 38% of patients with FTD had 1 or more first-degree relatives with dementia.²³ Duplication of the population-based study of Stevens et al²³ is more difficult in the United States, where the medical care system does not easily lend itself to a broad population-based study of FTD.

More than a third of affected first-degree relatives from families with autosomal dominant transmission in

the present study developed dementia with marked behavioral changes, paralleling the manifestations seen in index cases. Lynch et al¹ similarly reported personality change as the initial manifestation in all affected individuals within a DDPAC kindred. Among families with autosomal dominant transmission, 14 affected relatives (33%) had received psychiatric diagnoses; one third of these had major depression. Others had ALS or parkinsonism. Amyotrophic lateral sclerosis has been recognized as a common associated feature in a subset of families with FTDP in the literature.^{1,20}

The age of onset was younger than 65 years in the vast majority of index cases and affected relatives. The sex of the patient and the affected parent and the inheritance pattern did not affect the onset age. As described in previous individual case reports,^{2,4,19-21,24,25} our calculated penetrance in the fifth and sixth decades varied widely among families but was high. Although the majority of affected relatives (56 [93%] of 60) had initial symptoms prior to the age of 65 years, 4 affected relatives from 2 pedigrees had later onset. Other affected individuals in the 2 pedigrees manifested symptoms before the age of 65 years and at least 1 diagnosis was pathologically confirmed, reducing the likelihood that those with late onset had a dementia other than FTD.

Because FTD accounts for as many as 9% to 20% of dementias,^{26,27} it is among the most common heritable causes of presenile dementia. Other relatively common heritable but more rare early-onset dementias include early-onset familial Alzheimer disease, Creutzfeldt-Jakob disease, progressive supranuclear palsy, Parkinson disease with dementia, and pure Lewy body disease.²⁸⁻³⁰ No autopsy-derived prevalence estimates for the other heritable early-onset dementias have been published.

Interpretation of this study's results was limited by several sources of potential bias. Patients in the study were referred to a tertiary care clinic. The patients did not present for evaluation on the basis of involvement of multiple family members. In fact, all the individuals were unaware of the significance or relevance of positive family history at the time of presentation. Families usually expected that other affected relatives would manifest dementia with marked personality changes, but they need to be educated that ALS, mood disorders, and parkinsonism are also related to FTD.

Misdiagnosis can create type I errors, but the antemortem UCLA Alzheimer's Disease Center diagnostic accuracy surpassed 90%.¹⁶ Neuropathological biopsy or autopsy findings were identical to those in the FTD kindreds summarized by Foster et al.¹ However, diagnoses of affected relatives could not be confirmed by medical record review in all cases and depended on the family members contacted. We also relied on family members to provide onset ages, but the insidious nature of behavioral changes makes determining the onset of symptoms difficult to pinpoint. This would tend to increase the age of onset and decrease observed penetrance in early decades. Wherever possible, onset ages were confirmed by medical records or cross-referencing between 2 informants.

Early signs of FTD often include psychiatric conditions, such as alcoholism or depression, that are relatively common in the general population. Thus, some

affected individuals may represent phenocopies. Furthermore, familial cases of Parkinson disease, alcoholism, and ALS have been described in the literature.²⁹⁻³⁵ Some of the affected individuals in our study may actually represent a phenocopy or comorbidity of sporadic or familial cases of ALS or Parkinson disease, although it is unlikely that such cases were frequent enough to significantly alter our results.

To avoid overinclusion caused by co-occurrence of common disorders, we did not qualify an isolated diagnosis of alcoholism as an FTD symptom. However, inclusion of alcoholics and others with a history of substance abuse did not change the mode of inheritance and penetrance in any families. Depression accounted for one third of the psychiatric diagnoses, occurring in 8 patients from 7 families. Phenocopies owing to depression were a more likely source of type I errors than alcoholism, but the effect was not large, diminishing the incidence of families with an affected first-degree relative from 45% to 40%. The familial occurrence of depression is common, but familial depression usually has an earlier onset (third and fourth decades) than FTD-related disorders (fifth and sixth decades). In addition, autosomal dominant transmission has been discussed much more frequently in families with bipolar disorder than in families with major depression, supporting our inclusion of depression as an indicator of the status of the affected individual.³⁴⁻³⁶

Recently discovered tau mutations in a subset of families with FTD linked to chromosome 17 will make it possible to perform molecular diagnosis in some of the families in our sample.³⁷⁻⁴⁰ The extent to which tau mutations are causal in familial FTD remains to be determined. Tau mutations were found in some but not all FTD kindreds analyzed by Foster et al¹ and Poorkaj et al³⁸ and in only 25% of those recently reported by Hutton et al.⁴⁰

In addition to segmentation of neuropathological characteristics along the anterior-posterior axis, one of the unique features of FTD is its often lateralized asymmetric presentation. For example, FTD may present as hereditary dysphasic dementia in one family and right-sided degeneration in another. How tau pathological characteristics might cause the frontal vs temporal lobar pathologic characteristics or the strikingly lateralized presentation observed in some families remains an intriguing issue.

Accepted for publication October 21, 1998.

This study was supported by an Alzheimer's Disease Center grant (AG10123) from the National Institute on Aging, and a K08 grant (NS 01849; Dr Geschwind) from the National Institute of Neurological Disorders and Stroke, Bethesda, Md.

The authors gratefully acknowledge the participation and contribution of patients and their families. We also thank Jeffrey L. Cummings, MD, for his support and editorial contributions. Wendy Drain assisted in data collection and initial pedigree development.

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Reprints not available from the author.

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