Hereditary Frontotemporal Dementia Is Linked to Chromosome 17q21–q22: A Genetic and Clinicopathological Study of Three Dutch Families

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Hereditary frontotemporal dementia (HFTD) is a rare autosomal dominant form of presenile dementia characterized by behavioral changes and reduced speech. Three multigeneration kindreds with this condition, in the Netherlands, were investigated for clinicopathological comparison and linkage analysis. Frontotemporal atrophy on computed tomographic scanning and/or magnetic resonance imaging was usually present. Single-photon emission computed tomography (SPECT) showed frontal hypoperfusion in the early phase of the disease. Brain tissue showed moderate to severe atrophy of frontal and temporal cortex with neuronal loss, gliosis, and spongiosis. Pick bodies were lacking in all cases of the 3 families. The mean age of onset varied significantly between families. We report here evidence for linkage to chromosome 17q21–q22 with a maximum lod score of 4.70 at $\Theta = 0.05$ with the marker D17S932. Recombination analysis positions the gene for HFTD in a region of approximately 5 cM between markers D17S946 and D17S791. Three other neurodegenerative disorders with a strong clinical and pathological resemblance have recently been mapped to the same chromosomal region, suggesting that a group of clinically related neurodegenerative disorders may originate from mutations in the same gene.

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Hereditary frontotemporal dementia (HFTD) is the familial form of frontotemporal dementia (FTD), a rare, mostly sporadically occurring and predominantly presenile dementia [1–4]. The characteristic frontal and temporal lobar atrophy was originally described by Arnold Pick in 1892 [5]. Gans [6] in 1923, and later others, reported families with an autosomal dominant inheritance pattern [7–10]. A diagnosis of Pick's disease, the best known type of FTD, is now set aside for cases with so-called Pick bodies [11, 12], and several authors introduced diagnostic descriptions for new entities of frontal atrophy without Pick bodies [13–17]. The main clinical features of FTD are personality changes, a disinhibited and inappropriate behavior, hyperorality, stereotyped and perseverative behavior, emotional and social indifference, aspontaneity, loss of judgment and insight, and speech reduction [1, 13]. Molecular genetic studies of HFTD failed to find mutations in the genes implicated in Alzheimer's disease or the mutation in the prion protein gene involved in Creutzfeldt-Jacob disease [18–20]. More recently, linkage to chromosome 17 has been reported in a family with disinhibition–dementia–parkinsonism–amyotrophy complex (DDPAC), 2 families with progressive subcortical gliosis (PSG), and a family with pallido–ponto–nigral degeneration (PPND) [21–23]. The disease in these families shows a strong clinical and pathological resemblance to HFTD, as reported in this study [24–26].

To investigate whether HFTD could also be linked to the same region on chromosome 17q21–q22, we performed a linkage study with 3 large families with

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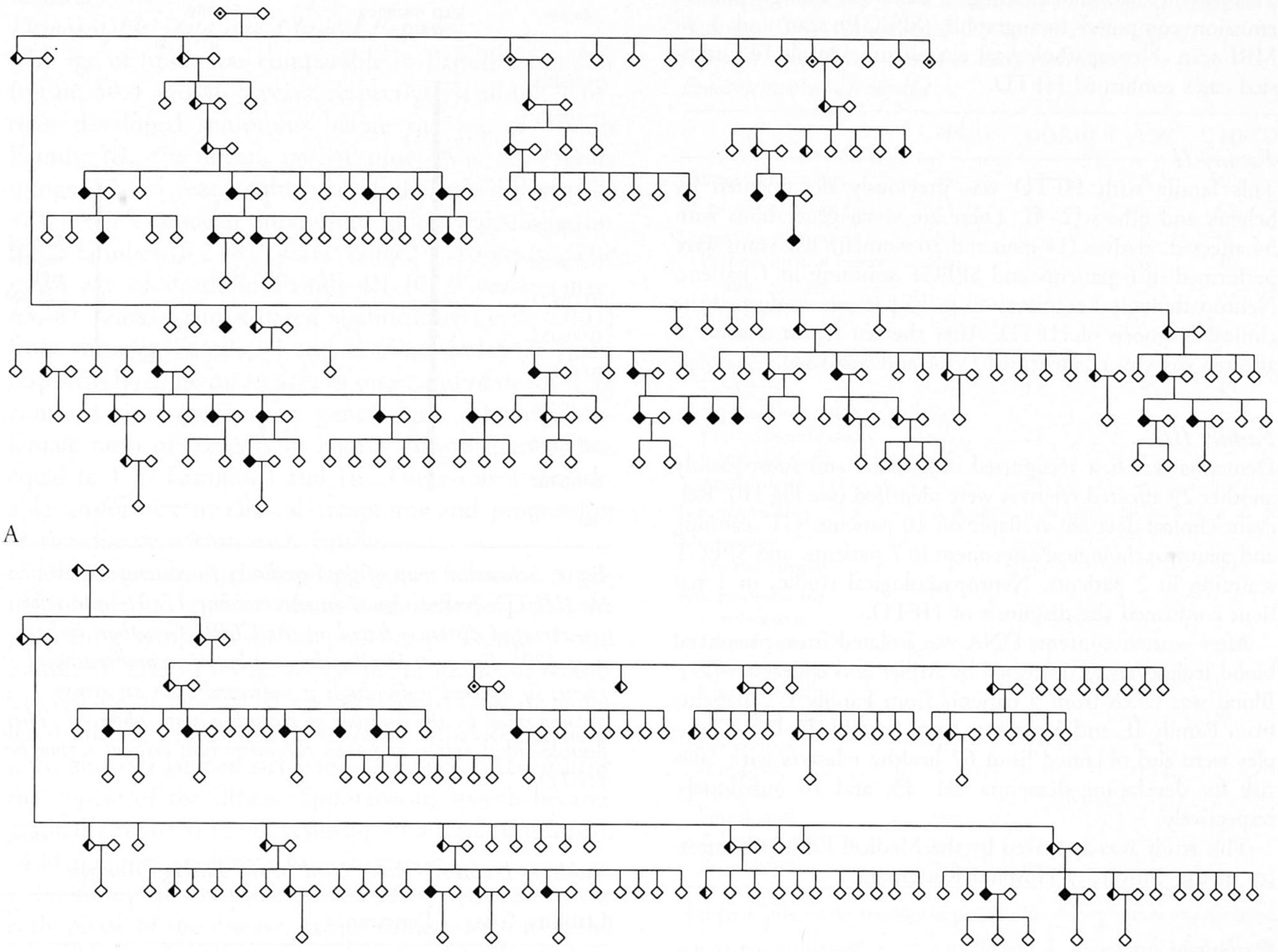

A

B

Fig 1. (A) Pedigree of Family I. (B) Pedigree of Family III. As the disorder shows clear autosomal dominant inheritance, sex designation of family members has been omitted for privacy reasons. ◇ = unaffected; ◇ = two different spouses; ◇· = possibly affected; ◆◇ = affected (dementia); clinical information insufficient to establish diagnosis FTD; ◆ = affected (fronto-temporal dementia); sufficient clinical information and/or pathologically confirmed.*

HFTD that were ascertained in the Netherlands. Here, we report evidence for linkage of HFTD to chromosome 17q21–q22, the same chromosomal region where DDPAC, PPND, and PSG have previously been localized.

Materials and Methods

Family Studies

In a genetic–epidemiological study of FTD in the Netherlands, we aimed to obtain a full ascertainment of FTD patients by addressing all neurologic, psychiatric, geriatric, and nursing homes to report their patients twice a year. In this study, 2 large families (Families I and III) with dementia were identified, whereas a third one (Family II) was reexamined. These families were selected for linkage analysis because of their strong clinical and pathological similarities. The second family has been described before as hereditary Pick's disease, despite the absence of Pick bodies [2–4]. Dementia is transmitted as an autosomal dominant disorder in all 3 families [4] (Fig 1B). The clinical picture in affected individuals meets the criteria for FTD [1]. The age at which behavioral changes were reported by more than 1 relative was considered as age of onset. Diagnosis of living patients was established using extensive neuropsychological testing and brain computed tomographic (CT) scanning and/or magnetic resonance imaging (MRI); diagnosis of deceased patients was established either on pathology findings or on available medical records and family interviews.

Family I

The first family consists of 2 sisters with dementia in the first generation and 49 of 160 offspring (28 men and 21 women) of these 2 sisters in the subsequent five generations (see Fig 1A). The diagnosis of FTD was established in 8 living patients. Sufficient clinical information and family history were available on 18 affected relatives to allow establishing age of onset and diagnosis of HFTD, whereas the type of dementia could not be specified by lack of detailed information in the remaining affected family members. A neuropsychological assessment was performed in 15 of 18 patients.

Ten patients had CT scanning; 3 cases had a single-photon emission computed tomographic (SPECT) scan and 3 an MRI scan. Neuropathological examination in all 14 autopsied cases confirmed HFTD.

Family II

This family with HFTD was previously documented by Schenk and others [2–4]. There are seven generations with 34 affected relatives (14 men and 20 women). CT scans were performed in 6 patients and SPECT scanning in 1 patient. Neuropathological examination in 15 patients confirmed the clinical diagnosis of HFTD. After the last report another 2 affected cases were identified (V14 and V21) [4].

Family III

Dementia was first recognized in 1 male, and subsequently another 29 affected relatives were identifed (see Fig 1B). Relevant clinical data are available on 10 patients, CT scanning and neuropsychological assessment in 7 patients, and SPECT scanning in 2 patients. Neuropathological studies in 1 patient confirmed the diagnosis of HFTD.

After written consent, DNA was isolated from peripheral blood leukocytes as described by Miller and colleagues [27]. Blood was taken from 5 patients from Family I, 2 patients from Family II, and 5 patients from Family III. DNA samples were also obtained from 62 healthy relatives with 50% risk for developing dementia (31, 15, and 16 individuals, respectively).

This study was approved by the Medical Ethics Committee of the University Hospital Rotterdam.

Pathology

Brain specimens of different cortical regions, basal ganglia, and pons from 11 cases (5 from Families I and II each, and 1 from Family III), were reexamined for Pick bodies, ballooned cells, and immunohistochemical features. Immunohistochemistry included the following antibodies: ubiquitin (1:125; Novocastra), τ (1:400; Dako, no. A 024), an antibody against paired helical filaments (PFHs) (1:100; ICN), an antibody against somatodendritic microtubule-associated protein (MAP-2) (1:170; Zymed), and β-amyloid antibody (1:600; Novocastra). Staining with a conventional peroxidase anti-peroxidase method was done. Age- and sex-matched controls (normal and with Alzheimer's disease) were used for comparison.

DNA Studies

Simple sequence length polymorphisms (SSLPs) from chromosome 17q21–q22 were amplified from 50 ng of genomic DNA. One primer from each pair was end labeled with [γ-^{32}P]ATP using T4 polynucleotide kinase. The amplification was performed essentially as described [28] except for markers D17S946 and D17S932 for which 7.5% dimethyl sulfoxide was added to the reaction mix. Analysis of SSLPs was performed on a denaturing 6% acrylamide gel.

Chromosome 17 markers were obtained from the CEPH/Genethon linkage map [29]. Marker order was obtained by combining data from the CEPH/Genethon linkage map and the Whitehead physical map [30] and is shown in Figure 2.

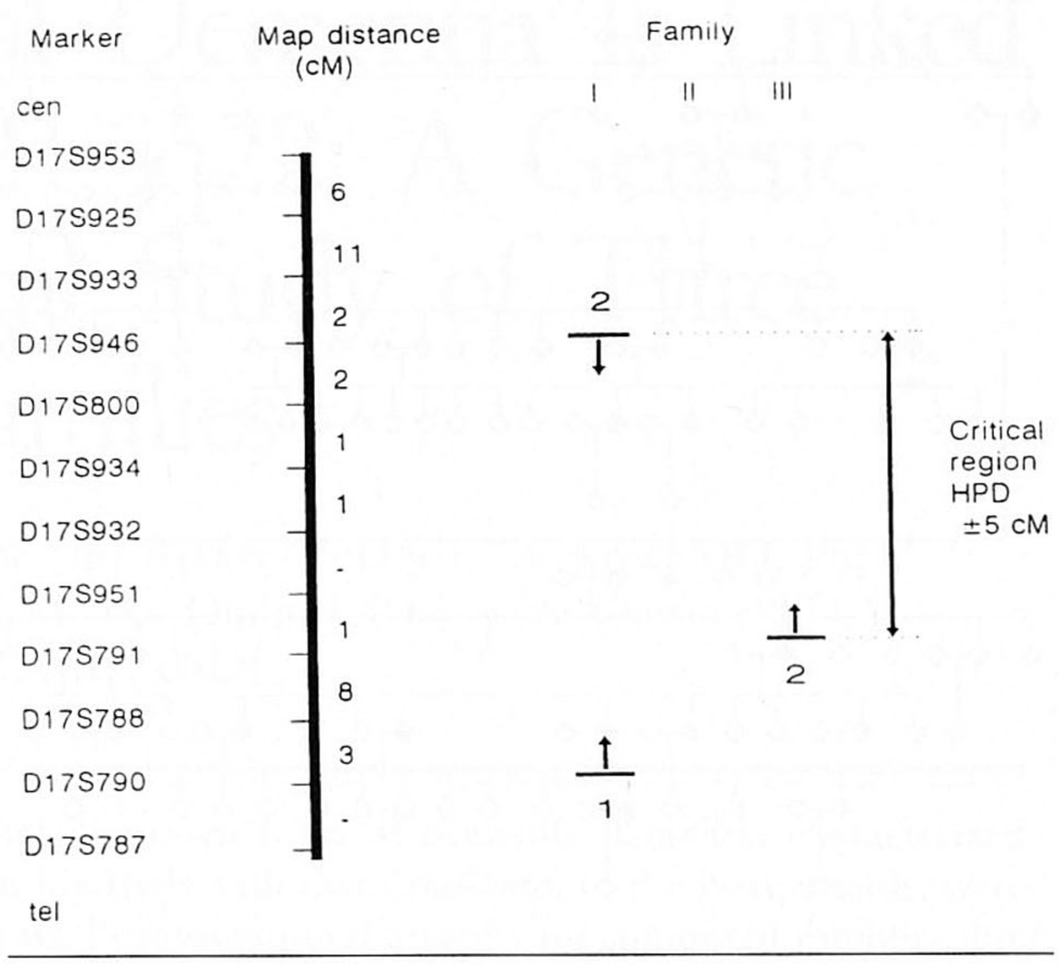

Fig 2. Schematic map of the hereditary frontotemporal dementia (HFTD)-linked region on chromosome 17q21–q22 with sex-averaged distances based on the CEPH/Genethon linkage map [29]. For each family, the number of recombinational events in affected individuals is indicated with an arrow *accompanied by the number of recombinations observed. The* double-sided arrow *indicates the minimum critical region for HFTD.*

Table 1. Liability Classes Used in the Linkage Analysis

Liability Class	Penetrance
Class 1	1.00 < married in or affected
Class 2	0.95 < unaffected, at risk >50 yr
Class 3	0.75 < unaffected, at risk, between 40 and 50 yr
Class 4	0.10 < unaffected, at risk <40 yr

Linkage Analysis

Pairwise lod scores were calculated for each family by using the MLINK program of the LINKAGE programs package (version 5.1) [31], assuming HFTD to be an autosomal dominant disease with a gene frequency of 0.0001. The mean age of onset in the available families was 51 years (range, 43–75 years). The late age of onset was accounted for by defining 4 liability classes with different penetrance values (Table 1). Phenocopy rate was estimated to be 0.1% for individuals older than 50 years of age and 0.01% for individuals younger than 50 years of age. Mutation rate was set at zero and equal recombination rates for males and females were assumed because of the variable recombination ratio between males and females in this region [29, 30]. Marker allele frequencies were kept equal because allele frequencies from the Dutch population were not available. Calculation of pairwise lod scores with allele frequencies calculated from individuals marrying into the HFTD kindreds did not substantially alter results (<10%).

Results

Demographic Data and Clinical Features

The age of onset was comparable in Families I and II (mean, 50.4 and 46.5 years, respectively); all but 1 patient developed symptoms before the age of 57. In Family III, the mean age of onset was 63.4 years (range, 57–75 years), which is significantly different ($p < 0.001$). The mean duration of illness was similar for the 3 families (8.2–8.7 years; range, 4–16 years). The mean age of death in Family III (71.9 years; range, 63–81 years) again differed significantly ($p < 0.001$) from those in Families I and II (58.6 and 54.7 years, respectively). The mean ages of onset and of death were constant over consecutive generations. The male-to-female ratio of patients in Family II was 2 to 5, but equal to 1 in Families I and III. There was a remarkable uniformity in clinical symptoms and progression of the disease within each family.

Disinhibition, including aggressive behavior, stealing, jocularity, and/or obsessional behavior, was the presenting symptom in all patients of Family I and Family II. Loss of initiative was the prominent presenting feature in Family III and developed later in Families I and II. Hyperorality, roaming behavior, restlessness, and stereotyped behavior developed often during the course of the illness. Spontaneous speech became gradually reduced in all, resulting in a state of mutism. Mild memory problems were common.

Neurological examination was always normal in the early phase of the disease, except sometimes for frontal release reflexes. The progression of the disease was quite similar in these families. Pyramidal and extrapyramidal signs occurred in several patients in the late phase of the disease (Table 2). Neuropsychological assessment showed frontal dysfunction in all patients of the 3 families. Perseveration, impaired attention, decreased mental shifting, impaired executive skills, and speech reduction reflecting frontal lobe dysfunction were found in combination with intact orientation and memory functions at neuropsychological assessment.

Electroencephalography, serum levels of vitamins, syphilis reactions, and/or thyroid function tests, performed in most patients, were always normal. CT scanning after a mean duration of illness of 2.5 years (range, 1–5 years) showed frontal atrophy (mild in 6, moderate to severe in 9 patients) in 15 cases from the 3 families, whereas CT scan was normal in 4 patients. Increased signal intensities in the subcortical white matter of the frontal lobe on T2-weighted MRI images were found in 2 patients of Family I. Frontotemporal hypoperfusion on SPECT was found in all 6 investigated patients.

The brain weights at autopsy from Families I and II were strongly reduced (mean, 1,035 and 920 gm, respectively); 1 case of Family III was 1,170 gm. Moderate to severe atrophy of the frontal lobe was present

Table 2. Comparison of Clinical and Pathological Features Between Three Chromosome 17–linked Neurological Disorders and Three Families with Hereditary Frontotemporal Dementia

	PPND	DDPAC	PSG	HFTD
Number of patients	26	12	8	49
Mean age of onset (yr)	43	45	46	51
Presenting symptoms				
Personality and behavioral changes	10	12	6	49
Dementia	5	–	–	–
Parkinsonism	14	1	–	–
Subsequent manifestations				
Dementia	26	12	8	49
Supranuclear palsy	15	–	–	–
Extrapyramidal signs	25	11	7	10
Pyramidal signs	16	3	1	7
Amyotrophy	–	1	–	–
Neuropathology	n = 4	n = 6	n = 7	n = 30
Macroscopy				
Frontal atrophy	4*	6	7	30
Microscopical involvement				
Frontal cortex	∓	++	++	++
Temporal cortex	∓	++	++	++
Caudate nucleus	+	nm	∓	+
Substantia nigra	4	6	4	9
Hippocampus	∓	∓	+	–
Amygdala	∓	++	nm	∓
Thalamus	∓	nm	∓	∓
Spinal cord	nm	∓	∓	–
Ballooned cells	nm	+	–	+
Pick bodies	nm	nm	–	–

Numbers indicate the number of patients for whom feature was observed.

nm = not mentioned; – = not affected; ∓ = not generally affected; + = generally affected; ++ = prominently affected; * = mild generalized atrophy described. PPND = pallido–ponto–nigral degeneration; DDPAC = disinhibition–dementia–parkinsonism–amyotrophy complex; PSG = progressive subcortical gliosis; HFTD = hereditary frontotemporal dementia.

in all cases of Families I to III, as well as atrophy of the anterior part of the temporal lobe. The caudate nucleus was atrophied in 9 cases of Families I and II each, and in 1 patient of Family III. Neuronal loss, gliosis, and spongiosis were found in the frontal and temporal cortex, in the absence of senile plaques and neurofibrillary tangles. The substantia nigra was degenerated in 4 brains of Families I and II each, and in 1 patient of Family III. Neuronal loss in the olivary nuclei was found in 3 brains. Some cases of Families I and II showed white matter changes (demyelination and/or gliosis). Ballooned cells in the cortex and/or basal ganglia were found in a number of cases of Families I and II, whereas these cells were absent in 1 case of Family III. Pick bodies were lacking in brains of the 3 families, except sporadically in 1 brain from Family II. At reexamination of 10 available brain specimens, no Pick bodies were found at all. Immunohistochemical studies were negative for τ or ubiquitin. In 2 pa-

Table 3. Two-Point Lod Scores for Chromosome 17 Markers and HFTD

Marker	Family	Recombination Fraction (Θ)						
		0.000	0.010	0.050	0.100	0.200	0.300	0.400
D17S953	I	−3.96	−1.31	−0.59	−0.29	−0.04	0.02	0.08
	II	−1.29	−1.14	−0.77	−0.52	−0.25	−0.10	−0.02
	III	−2.18	−1.96	−1.35	−0.87	−0.36	−0.12	−0.02
	Total	−7.43	−4.41	−2.71	−1.68	−0.65	−0.20	−0.04
D17S925	I	−0.43	−0.37	−0.19	−0.05	0.07	0.08	0.05
	II	−8.16	−1.21	−0.54	−0.29	−0.10	−0.03	−0.01
	III	−1.89	−1.70	−1.17	−0.76	−0.30	−0.08	0.01
	Total	−10.48	−3.28	−1.90	−1.10	−0.33	−0.03	0.05
D17S933	I	−3.55	−1.33	−0.63	−0.34	−0.14	−0.06	−0.01
	II	−8.14	−0.63	−0.02	0.16	0.20	0.11	0.03
	III	−0.96	−0.83	−0.46	−0.21	0.00	0.04	0.01
	Total	−12.65	−2.79	−1.11	−0.41	0.06	0.09	0.03
D17S946	I	1.88	1.84	1.67	1.43	0.95	0.48	0.12
	II	0.34	0.33	0.29	0.24	0.17	0.10	0.04
	III	−2.30	−1.96	−1.20	−0.71	−0.24	−0.06	−0.01
	Total	−0.08	0.21	0.76	0.96	0.88	0.52	0.15
D17S800	I	−0.35	−0.32	−0.23	0.14	−0.04	0.00	0.01
	II	−0.18	−0.18	−0.15	−0.12	−0.07	−0.03	−0.01
	III	0.92	0.94	0.98	0.96	0.77	0.47	0.15
	Total	0.39	0.52	0.60	0.70	0.66	0.44	0.15
D17S934	I	2.76	2.71	2.50	2.22	1.58	0.91	0.32
	II	1.35	1.33	1.23	1.10	0.82	0.49	0.16
	III	0.17	0.20	0.27	0.26	0.16	0.05	−0.02
	Total	4.28	4.24	4.00	3.58	2.56	1.45	0.46
D17S932	I	2.64	2.59	2.38	2.10	1.49	0.86	0.29
	II	1.61	1.57	1.44	1.27	0.90	0.50	0.14
	III	−3.98	0.36	0.89	0.96	0.79	0.47	0.14
	Total	0.27	4.52	4.71	4.33	3.18	1.83	0.57
D17S951	I	2.07	2.05	1.93	1.74	1.26	0.71	0.21
	II	0.68	0.67	0.61	0.53	0.37	0.21	0.07
	III	−0.45	−0.29	0.08	0.27	0.34	0.22	0.07
	Total	2.30	2.43	2.62	2.54	1.97	1.14	0.35
D17S791	I	1.55	1.54	1.42	1.25	0.85	0.46	0.16
	II	0.80	0.77	0.68	0.57	0.38	0.21	0.07
	III	−5.12	−0.70	0.05	0.31	0.38	0.25	0.08
	Total	−2.77	1.61	2.15	2.13	1.61	0.91	0.31
D17S788	I	−2.81	−0.79	−0.17	0.03	0.12	0.08	0.02
	II	−∞	−0.42	0.17	0.34	0.36	0.23	0.07
	III	−13.03	−2.86	−1.35	−0.72	−0.19	−0.02	0.01
	Total	−∞	−3.27	−1.35	−0.35	0.29	0.29	0.10
D17S790	I	−1.82	−0.02	0.60	0.77	0.73	0.48	0.18
	II	−∞	−0.20	0.38	0.53	0.50	0.33	0.12
	III	−5.62	−1.43	−0.74	−0.45	−0.19	−0.09	−0.03
	Total	−∞	−1.65	0.24	0.85	1.04	0.72	0.27
D17S787	I	2.60	2.57	2.43	2.20	1.65	1.02	0.39
	II	−∞	−0.41	0.18	0.35	0.37	0.24	0.08
	III	−8.40	−2.46	−1.47	−0.92	−0.35	−0.11	−0.03
	Total	−∞	−0.30	1.14	1.63	1.67	1.15	0.44

HFTD = hereditary frontotemporal dementia.

tients scattered mild diffuse and granular staining for MAP-2 was visible in both neurons and glia.

Linkage

Three linkage reports [21–23] of variable forms of frontal lobe dementia prompted us to investigate whether the families with HFTD described in this study were linked to the same region on chromosome 17q21–q22. We selected 12 SSLPs from the CEPH/Genethon linkage map. There was a discrepancy in marker order between the CEPH/Genethon linkage map and the Whitehead physical map for markers D17S932 and D17S934 [29, 30]. In our study we used the marker order obtained by physical mapping data from the Whitehead map. Positive lod scores were obtained for a number of markers in the region for all 3 families. Table 3 summarizes the pairwise lod scores between HFTD and the 12 chromosome 17q markers. None of the individual families was powerful enough to provide significant evidence for linkage by itself, but with the combined data of the 3 families significant lod scores were obtained for the marker D17S932 ($Z = 4.70$ at $\Theta = 0.05$) and D17S934 ($Z = 4.28$ at $\Theta = 0.00$).

A substantial part of the information that contributed to these lod scores in these families comes from unaffected individuals that are at risk for the disease. We therefore reanalyzed D17S932 and D17S934, giving all the unaffected individuals a diagnosis unknown. The maximum lod score obtained with this analysis for marker D17S932 was 2.99 at $\Theta = 0.00$. For marker D17S934, the maximum lod score obtained was 3.46 at $\Theta = 0.00$.

The marker order and intermarker distances of the available genetic and physical maps do not always concur. Therefore multipoint linkage analysis can generate a confidence interval that later would prove to be inaccurate. To strengthen our findings, we performed haplotype analysis for all 12 markers positioned according to the physical map. In a number of cases the haplotype of the markers for the affected individuals could not be determined because of the unavailability of first-degree relatives (data not shown). As a result it could not be determined whether marker alleles were identical by descent (IBD) or just identical by state (IBS). To determine the size of the critical region for the gene responsible for HFTD, we therefore compared marker data for affected individuals only (Fig 3A–C).

The 5 patients from Family I share a common allele for 6 of the markers tested (see Fig 3A). On the centromeric side, no sharing was found for D17S953, D17S925, and D17S933, and D17S946. On the telomeric side, no sharing was obtained for D17S790 and D17S787. The 2 patients in Family II (see Fig 3B) share a common allele for all 12 markers that were tested, and no recombination event could be detected by comparing inherited alleles. The linkage analysis, however, revealed recombination events in this family for markers D17S788, D17S790, and D17S787 (see Table 3). In Family III (see Fig 3C), the patients share at least one allele for almost all markers except for markers D17S791, D17S788, and D17S787. At least two recombination events must have taken place in this family, since only 3 of 5 patients share a common allele for D17S791.

These data place the HFTD locus telomeric from D17S946 and centromeric from D17S791. The distance between both markers is 5 cM on the sex average linkage map (see Fig 2) [29]. A common ancestor for the 3 families could not be traced genealogically. The patients from the 3 families do not share a common disease haplotype. This indicates that HFTD in the 3 families is caused by independent mutational events.

Discussion

The 3 families with HFTD described in this study show strong clinical and pathological similarities. All patients presented with behavioral changes followed by mutism, and sometimes by pyramidal and/or extrapyramidal signs in the final phase. Selective atrophy of the frontal and temporal lobe is the characteristic feature on CT/MRI and at neuropathological examination in all 3 families. Anterior hypoperfusion on SPECT was a common finding. The unifying pathological feature in all 3 families was the selective frontotemporal atrophy with aspecific features. Although ballooned cells were present in some cases, Pick bodies were lacking in all.

There are also some clinical differences between the 3 families. The mean age of onset in Family III was significantly higher than in the other 2 families. Disinhibition was the presenting clinical symptom in Families I and II, but in patients of Family III, loss of initiative was the first symptom. Caudate atrophy, degeneration of the substantia nigra, and white matter involvement found in some brains of the 3 families might reflect intrafamilial phenotypical variation. Similar observations are reported in hereditary dysphasic dementia and other conditions with a descriptive diagnosis [16, 24, 26]. Ballooned cells were present in some brains of Families I and II. That they were lacking in the only autopsied case of Family III does not indicate a pathological distinction from Families I and II, since ballooned cells were not found in several brains from these families either.

Family II has been cited as hereditary Pick's disease (HPD) in McKusick Mendelian Inheritance of Man [32]. However, if Pick bodies are essential for diagnosis of Pick's disease, according to the criteria, this family should not be considered to have Pick's disease, since Pick bodies were lacking in all cases. It is even doubtful if other earlier reported families did have HPD, since

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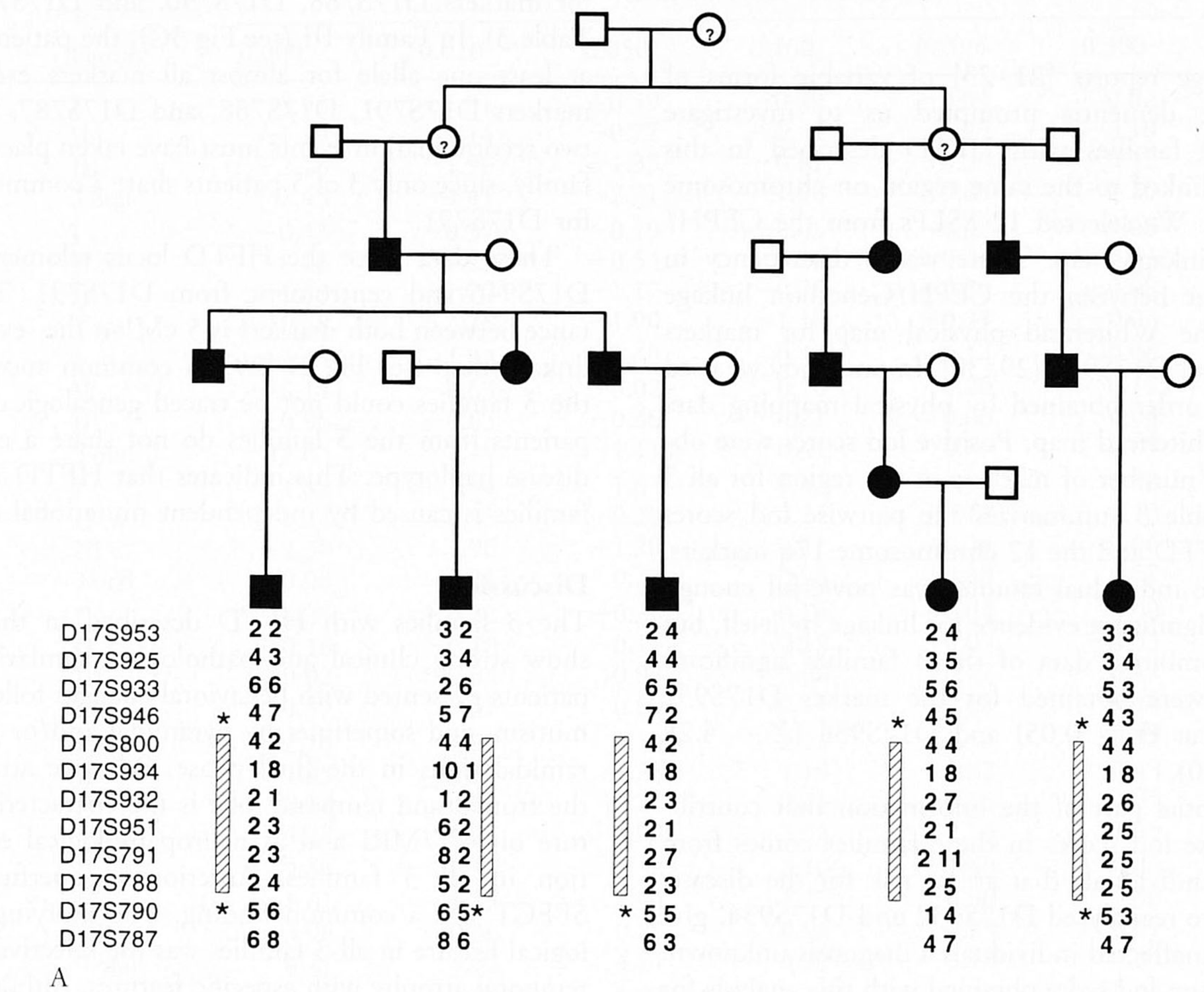
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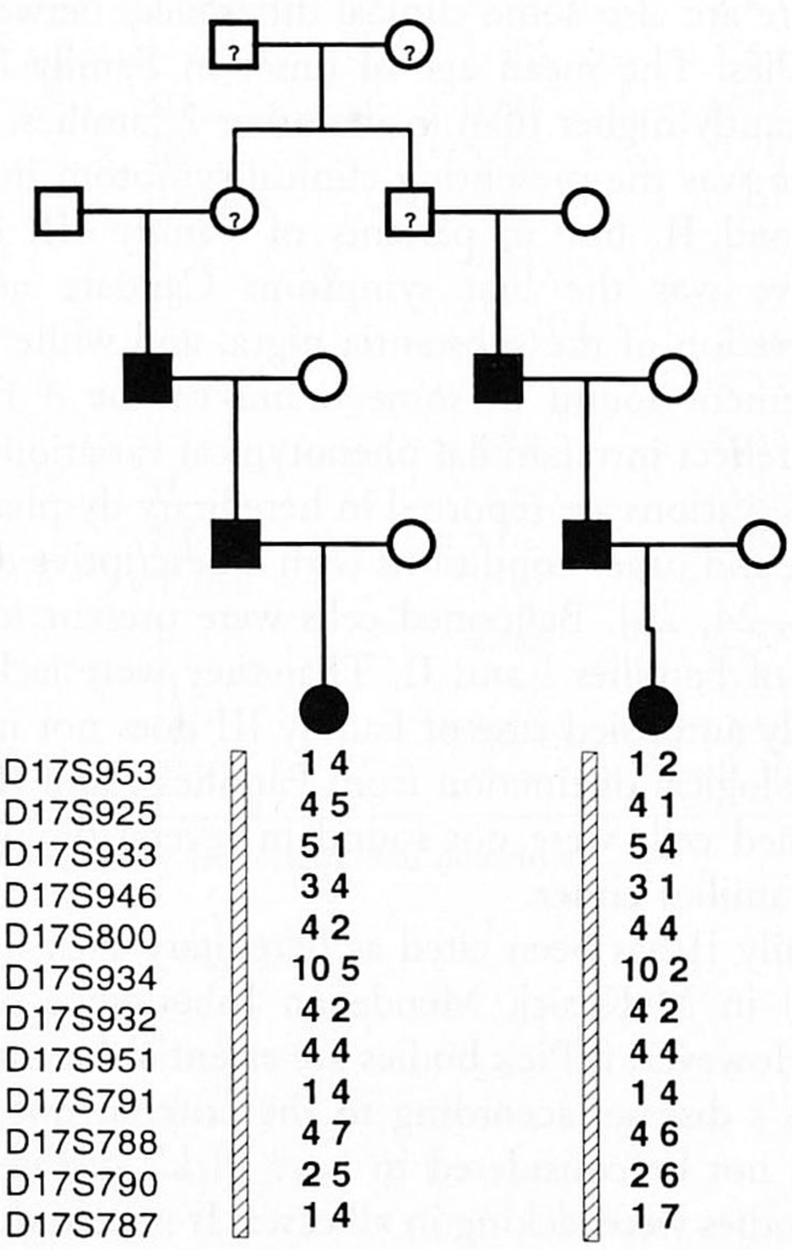
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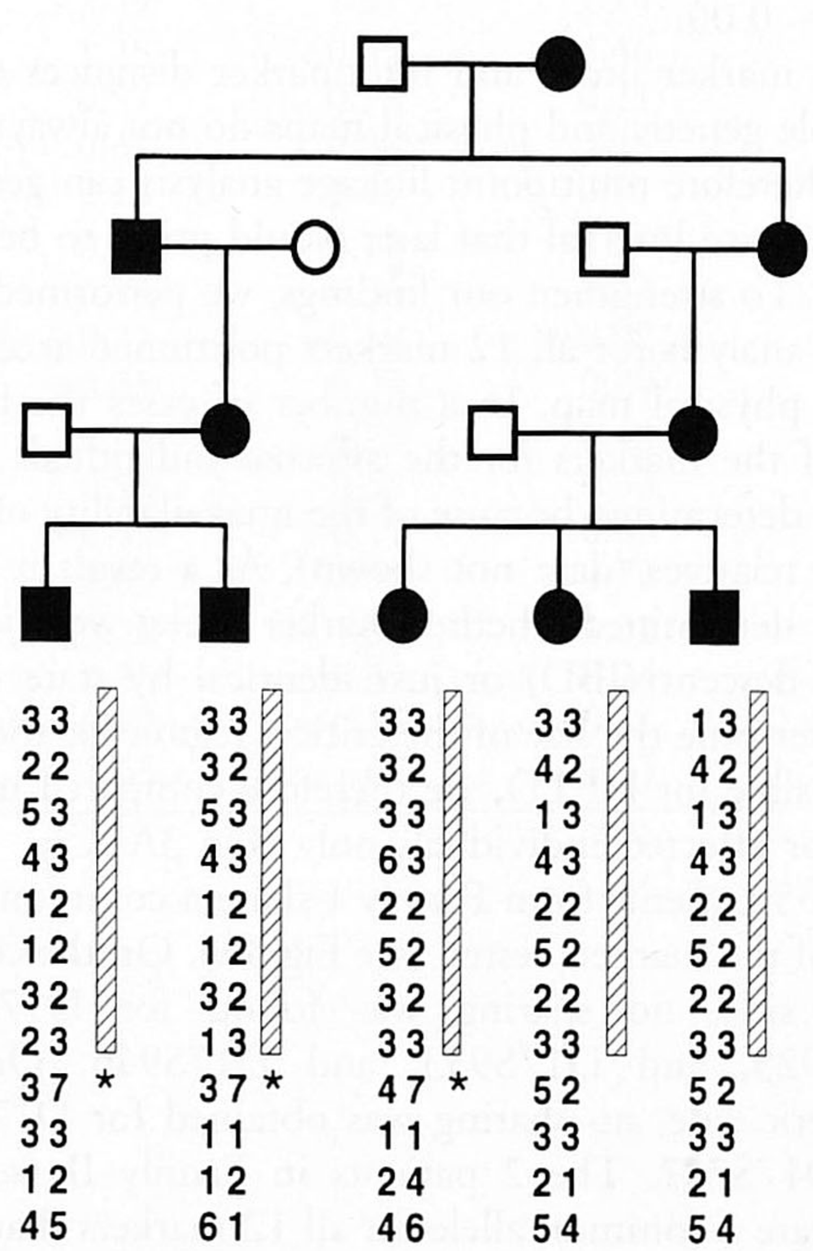
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3 3 3 2 3 3 6 3 2 2 5 2 3 2 3 3 4 7 * 1 1 2 4 4 6
3 3 4 2 1 3 4 3 2 2 5 2 2 2 3 3 5 2 3 3 2 1 5 4
1 3 4 2 1 3 4 3 2 2 5 2 2 2 3 3 5 2 3 3 2 1 5 4

most of these families did not show Pick bodies [7–10]. Taking into account the contribution of Arnold Pick to the recognition of this type of dementia [5], one might also redefine and reintroduce the diagnosis of Pick's disease for all cases with frontotemporal atrophy. In that case, frontal atrophy with Pick bodies should be considered a subtype.

We report linkage of HFTD in 3 Dutch families to chromosome 17q21–q22. All families generated positive lod scores with several markers from this chromsomal region. None of the families is informative enough to generate a significant lod score by itself, but combining the data from all families gives significant evidence for linkage. The clinical heterogeneity of Family III compared with Families I and II is not reflected in the linkage results. Family III also generated positive lod scores for a number of markers (see Table 3). Two unaffected individuals in this family share part of the haplotype that is found in patients (data not shown). These individuals are 70 and 75 years of age respectively, and in the linkage analysis we assumed 95% penetrance of the disease phenotype at that age. For this reason these individuals are regarded by the linkage program as likely recombinant cases, resulting in low lod score curves that had their peak at a considerable recombination value from markers. Considering the later onset of the disease in this family, the linkage parameters that were used are probably too conservative for this specific family. It is still unclear whether these individuals will still develop the disease phenotype. Further support that Family III is indeed linked to chromosome 17q21 comes from the fact that all 5 patients share a common allele for more than 20 cM on chromosome 17q21–q22 (see Figs 2 and 3C).

Comparison of marker alleles revealed recombination events in affected individuals with a number of markers. Recombination events with the markers D17S946 and D17S791 define the boundaries of the critical region. According to the CEPH/Genethon linkage map, these markers are separated by a genetic distance of approximately 5 cM. The 3 families do not share a common "disease" haplotype, suggesting that independent mutations are responsible for the onset of the disease in these families.

For a number of markers, it could not be determined whether the shared alleles were IBD or IBS. We are currently constructing hybrid cell lines of all available patients in order to separate the disease chromosome and the healthy chromosome. This will enable us to determine whether shared alleles are IBD or IBS. These data could reduce the critical region further.

A large number of genes have been localized on chromosome 17q. Several of them are involved in neurological functions or diseases and could be regarded as candidate genes for HFTD. Glial fibrillary acidic protein is an intermediate filament protein that is highly specific for cells of astroglial lineage (glial fibrillary tangles). The level of protein expression is elevated in patients with Alzheimer's disease, Down's syndrome, and scrapie infection [33–35]. The exact localization of this gene on chromosome 17q is unclear [36]. The nerve growth factor receptor (NGFR) is able to bind nerve growth factors and is an essential component in the survival and maintenance of sympathetic and sensory neurons [37, 38]. NGFR was located on a single restriction fragment of 500 kb with the HOX2B gene [39]. According to the mapping data in the Human Genome Database [40], the HOX2B gene is localized within the critical region for HFTD.

The microtubule-associated protein τ that was localized on the long arm of chromosome 17 appears to be involved in the maintenance of axonal cytoskeletal structure. The gene is expressed in neurons and its transcript is subject to alternative splicing and posttranscriptional modifications. These modifications can lead to the formation of the PHF, which is a major component of neurofibrillary tangles. Neurofibrillary tangles in Alzheimer's disease [41, 42] and neurofilaments in Pick bodies, as observed in sporadic patients with Pick's disease, stain intensively with antibodies against phosphorylated τ [43]. However, in brain tissue of cases of HFTD from this study, no Pick bodies were found; ballooned cells were observed, but they did not stain with antibodies against τ. Genetic mapping on radiation hybrids places τ between markers D17S190 and D17S409 [44]. These markers are not part of the CEPH/Genethon map that was used for this study, and it is difficult to determine whether τ or one of the other genes mentioned above is localized within the critical region. We are currently mapping these genes into the CEPH/Genethon linkage map by using the GeneBridge 4 radiation hybrid mapping panel [45].

This study demonstrates linkage in 3 families with HFTD to chromosome 17q21–q22. Recently, linkage

Fig 3. Marker data for chromosome 17q21–q22 markers for all available patients in the 3 families with hereditary frontotemporal dementia. Markers are oriented from the centromeric side to the telomeric side. The hatched boxes *indicate the maximum region of allele sharing between patients. *Alleles that are shared only by some patients in the family. Only relatives leading to a common ancestor are indicated. (A) Family I. (B) Family II. (C) Family III.* Filled symbols *represent affected individuals,* question marks *in symbols indicate that insufficient data were available to determine diagnosis,* open symbols *indicate unaffected individuals.*

was reported to the same region of the three hereditary neurological disorders with a very strong clinical and pathological resemblance (see Table 2): DDPAC [21], PSG [22], and autosomal dominant parkinsonism and dementia with PPND [23]. Now an important question is whether these chromosome 17q21–q22 disorders are caused by mutations in the same gene or whether there are different genes in this region that are responsible for these disorders.

The three conditions show considerable clinical and pathological overlap with HFTD in age of onset, presenting and subsequent symptoms, and most affected brain regions [24–26] (see Table 2). All four conditions share a presenile age at onset, and most patients show personality and behavioral changes as an initial manifestation. The mean age of onset between families varies, but this difference is smaller than the intrafamiliar differences in age of onset. Brain tissue reveals only general features of degeneration like neuronal cell loss and gliosis. Pick inclusion bodies are absent in all cases. Varying degrees of frontal lobe atrophy were present in all cases of DDPAC, PSG, and HFTD. In the PPND family, mild generalized atrophy with mild neuronal loss and gliosis was found. Degeneration of subcortical structures (caudate nucleus, hippocampus, and substantia nigra) showed a rather similar pattern in all families. There are, however, also some differences within the "chromosome 17 families." First, parkinsonism was the only presenting symptom in 14 of 26 affected family members of the PPND family but only in 1 of 69 patients of the other families. During the course of the disease, parkinsonism is also observed in the majority of the patients with DDPAC and PSG and in 10 of 49 patients with HFTD. The absence of parkinsonism in the majority of HFTD patients must be interpreted with caution because most patients had their neurological examination in an early phase of the illness. The actual frequency of parkinsonism might have been higher in later phase of the illness.

Second, 5 patients from the PPND family had dementia as the presenting symptom, whereas in the other families these were personality and behavioral changes. To determine if these manifestations show overlap requires a detailed comparison of clinical data. Finally, there was a significant difference in age of onset between the first 2 families and the third family of the present study. Even if there are some clinical and pathological differences between the phenotypes of HFTD, DDPAC, and PSG, these are no basis for a sharp differentiation into separate entities. Also the presentation of parkinsonism in PPND seems different from the other families, but it needs additional study to establish if this is phenotypic variation or locus heterogeneity.

At this moment it is unknown if these four conditions are genetically related. The published data do not allow definition of an overlapping critical region for the four disorders. The critical region for the responsible gene(s) for PSG and DDPAC has not yet been determined; multipoint linkage analysis for DDPAC suggested a localization between D17S800 and D17S787, but these borders are based on healthy "at risk" individuals and must be interpreted cautiously. The critical region for PPND was determined based on recombination events in affected individuals. This region, between markers D17S250 and D17S943, partly overlaps with the critical region for HFTD reported in this study.

The currently available data suggest that all four disorders might very well be caused by different mutations in the same gene or even by variant expressions of a single mutation. Another explanation might be different genes, localized in close proximity of each other, being responsible for the four linked neurological diseases. The answer to this question requires further dissection of this region and the identification of its genes.

In conclusion, HFTD is part of a group of neurodegenerative diseases with striking clinical and pathological similarities. The critical regions for all four disorders show considerable overlap on chromosome 17q21. The available clinical and genetic data suggest that this group of disorders might be considered phenotypic variants of the same disorder. The discussion of whether the group of "chromosome 17–linked neurological diseases" should be considered as separate entities, as subtypes of HFTD, or even hereditary Pick's disease, will only be resolved after the identification of the responsible gene defect for these disorders.

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