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Familial Multiple-System Tauopathy with Presenile Dementia Is Localized to Chromosome 17

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Summary

An autosomal dominant presenile dementia affecting 39 individuals in a seven-generation, 383-member pedigree has been studied at Indiana University. In the affected members of this family, clinical symptoms occurred early in life, with an average age at onset of 48.8 years. The presenting clinical features include disequilibrium, neck stiffness, dysphagia, and memory loss. As the disease progresses, further cognitive decline, superior-gaze palsy, and dystaxia also are observed. The average duration from onset of symptoms to death is ~10 years. Neuropathologic studies of nine affected individuals showed neuronal loss in several areas of the CNS, as well as argentophilic tau-immunopositive inclusions in neurons and in oligodendroglia. A limited genomic screen by use of DNA samples from 28 family members localized the gene for this disorder to a 3-cM region on chromosome 17, between the markers THRA1 and D17S791. The gene for tau also was analyzed, through samples from the family.

Introduction

Recently, five studies (Wilhelmsen et al. 1994; Brown et al. 1995; Wijker et al. 1996; Yamaoka et al. 1996; Heutink et al. 1997) have described seven large pedigrees with different autosomal dominant forms of presenile frontotemporal dementia. In one family, affected individuals had personality changes, and some members were diagnosed as having schizophrenia and parkinsonism (Wilhelmsen et al. 1994). This condition was named disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC). A second family showed a nonspecific dementia that has been linked to chromosome 3 (Brown et al. 1995). Pallido-ponto-nigral degeneration (PPND) with parkinsonism and dementia characterized the third family (Wijker et al. 1996). The fourth family was described as having a non–Alzheimer disease dementia (Yamaoka et al. 1996). Finally, three Dutch families with hereditary frontotemporal dementia characterized by behavioral changes and speech problems were described recently (Heutink et al. 1997). Six of these seven families are linked genetically to chromosome 17q21-22.

Clinically and pathologically these disorders appear to be distinct from one another. Although general findings, such as the absence of β-amyloid and a variability of neurofibrillary changes, have been described, extensive pathological studies have not been performed for most of these reported disorders.

We recently have described a seven-generation, 383-member pedigree with an autosomal dominant neurological disorder (Ghetti and Farlow 1994). In affected members of the family, the clinical symptoms appeared at an average age of 48.8 years (range 39–59 years), and the duration of the disease was 10 years. The initial clinical features included disequilibrium, neck stiffness, dysphagia, and memory loss. In later stages of the disease, further cognitive decline, dystaxia, and extrapyramidal signs, including marked superior-gaze palsy, were observed.

Neuropathological studies revealed neuronal loss in several cortical areas. These regions showed argentophilic tau-immunopositive inclusions. Twisted filaments composed of tau protein also were observed. These differed, in diameter and periodicity, from the paired helical filaments of Alzheimer disease (Spillantini et al. 1997). Because of the clinical and pathological characteristics of this family, the disease has been named "familial multiple-system tauopathy with presenile dementia" ("MSTD").

Determination of the genetic location of MSTD was deemed important for identification of the gene causing this disorder. Chromosome 17 was one logical location

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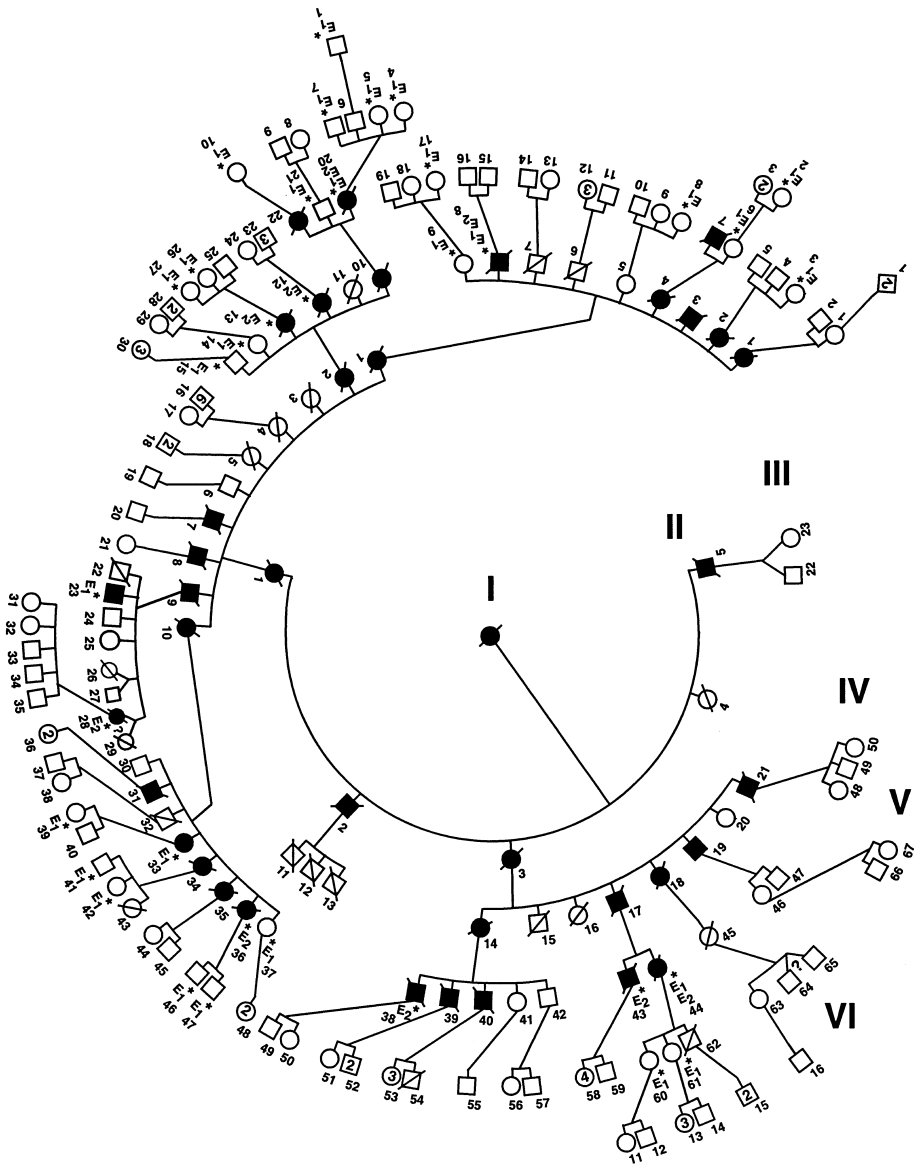

Figure 1 Pedigree of the MSTD family. Blackened symbols denote affected individuals. To obtain DNA samples, blood was drawn from all individuals who were clinically examined (indicated by "E_1"). "E_2" indicates those individuals on whom an autopsy was performed. An asterisk (*) indicates that an evaluation was documented.

to start a genetic screen, because of (1) the pathological involvement of tau and the fact that the tau gene is localized to 17q21-22 and (2) the fact that the other disorders also had been linked to the same chromosomal region as the tau gene. However, genetic screening of those chromosomes known to harbor genes that cause dementia also was undertaken for this family, in the hope that one of these locations possibly might provide linkage. The chromosomes associated with Alzheimer disease, familial nonspecific dementia (Brown et al. 1995), prion diseases, and the frontotemporal dementias were examined. This article presents the results of this genetic study and an analysis of the tau gene as a candidate for MSTD.

Material and Methods

Informed consent for these studies was obtained from the participating family members. A pedigree is shown in figure 1. Blood or tissue samples from 48 individuals were collected. Eleven of these samples were from affected individuals. Five of these 11 patients had been examined by a neurologist, and autopsies with neuropathologic evaluations had been performed on 9 of the

patients. Three affected individuals were examined both neurologically and pathologically. The diagnosis of MSTD was based on these neurological exams and/or neuropathological studies.

For the neuropathologic studies, tissue blocks and slides were prepared by use of methods described elsewhere (Ghetti et al. 1996). The 10-μm sections were incubated with monoclonal antibodies raised against tau, such as phosphorylation-dependent AT8, and PHF1 (1:500) and phosphorylation-independent Alz50 (1:500). For detection of the β-amyloid protein, the monoclonal antibody 10D5 (1:500) was used (Knops et al. 1991). The peroxidase-antiperoxidase method, using the peroxidase substrates 3,3′-diaminobenzidine and 0.015% H_2O_2, was used for immunodetection (Ghetti et al. 1992).

DNA samples from 28 members of the family were used for the genomic screen, because these samples provided the most information for the linkage analyses. Genotypic studies focused on a few candidate regions on chromosomes 1 and 3 and on the entire chromosome for chromosomes 14, 17, 19, 20, and 21. Microsatellite primer pairs were obtained from Research Genetics. Markers were selected either to span the whole chromosome of interest, with ~10-cM spacing, or to surround and include the disease-gene locus, within 10 cM, in the case of chromosomes 1 and 3.

Genomic DNA from blood samples was isolated by proteinase K digestion, phenol-chloroform extraction, and precipitation in isopropanol. Six DNA samples were obtained from histological sections, by use of the protocol described by Nichols et al. (1990). Markers were analyzed by the end-labeling of one primer, with [γ-^{32}P]ATP, and by use of this primer with a paired unlabeled primer, to amplify 20 ng of genomic DNA. The products were separated by use of 6%-polyacrylamide/8 M–urea gel electrophoresis. Gels were dried and were exposed to film. Allele sizes were determined by comparison with known alleles of CEPH parents 1331-01 and 1331-02; however, when the allele size was unclear, the sequence of a molecular-weight standard was used to determine exact size.

Examination of the pedigree clearly indicated autosomal dominant transmission of MSTD, in this family. All affected individuals have an affected parent, implying a highly, if not fully, penetrant disorder. In the family, the earliest age at onset was 39 years, and the latest age at onset was 59 years. Owing to the small number of individuals with a well-established age at onset in this family, a simple penetrance function was modeled, with zero penetrance from birth to age 35 years then an increase in a linear fashion until age 60 years, when the maximum penetrance of 99% is reached. The frequency of the disease gene was assumed to be 1/1,000 chromosomes in the population, and the LOD scores calculated were stable across order-of-magnitude changes in this estimate, as well as across changes in the penetrance function. Allele frequencies and recombination frequencies between loci used in the analyses were taken from the on-line CEPH-Généthon database (http://www.cephb.fr/bio/ceph-genethon-map.html), the Genome Database (http://gdbwww.gdb.org/), and the Cooperative Human Linkage Center database (http://www.chlc.org/). The frequencies of the marker alleles also were estimated for this family by use of the USERM13 subroutine of the MENDEL suite of programs. The allele-frequency estimates from this program were similar to those reported in the CEPH-Généthon database (http://www.cephb.fr/bio/ceph-genethon-map.html). The MLINK program from the FASTLINK, version 3.0, package (Schaffer et al. 1994) was used to perform pairwise LOD-score analysis.

Multipoint analyses were performed with the program VITESSE (O'Connell and Weeks 1995). Owing to the presence of multiple generations of nongenotyped persons, at the top of the pedigree, the family was split into two parts, so that the multipoint calculations would be computationally feasible. Two-point LOD scores were computed for the split pedigree, and, whereas the maximum LOD score for each marker was slightly decreased as compared with the maximum score for the pedigree analyzed in its entirety, all information regarding recombination was preserved. The nine most informative markers, spanning the region of chromosome 17 implicated by the two-point results, were included in the multipoint analyses. For the disease locus, likelihoods were calculated by use of three marker loci at a time, to keep the computation time reasonable (~1.5 d/calculation). A window of three marker loci was moved along the map of nine markers, one marker at a time, and multipoint analysis was performed for overlapping groups, each comprising three adjacent markers.

Sequencing of the tau gene was performed by direct sequencing, as described in the study by Nichols et al. (1990). Primers from the intronic sequences flanking each exon were used so that the entire exon sequence and the splice signals could be analyzed. Sequences were compared to that of a normal control and to the published tau-gene sequence.

Results

Linkage analysis was performed for this family. Because of the similarity of MSTD to other inherited dementias, chromosomes harboring genes associated with those dementias were analyzed. Most of the candidate regions, such as chromosomes 14, 19, 20, and 21, were excluded by use of two-point LOD scores of $\leqslant -2.00$ (data not shown). A 15-cM region (six markers) around the presenilin II gene on chromosome 1 and a 50-cM

Table 1

Two-Point LOD Scores Determined with Markers on Chromosome 17

Locus	θ[a] (cM)	LOD Score at Recombination Fraction of .00	.01	.05	.10	.20	.30	.40	Z_{max}	θ_{max}
D17S969	28.0	−4.22	−.83	−.24	−.08	−.01	−.01	−.01	.00	50.0
D17S798	3.0	−2.90	.76	1.31	1.37	1.12	.69	.26	1.38	8.8
D17S1293	4.0	−2.32	1.09	1.51	1.48	1.12	.68	.24	1.53	6.4
D17S946	3.0	−2.28	.54	1.07	1.15	.97	.64	.27	1.15	9.5
D17S250	2.0	1.63	1.59	1.42	1.22	.83	.47	.16	1.63	.0
THRA1	1.0	−3.40	−.08	.43	.50	.38	.21	.08	.50	9.6
D17S800	1.0	.41	.39	.34	.27	.15	.08	.03	.41	.0
D17S932	1.0	2.06	2.04	1.91	1.73	1.29	.79	.28	2.06	.0
D17S934	.0	.93	.88	.71	.50	.14	−.04	−.03	.93	.0
D17S951	.0	2.24	2.19	1.98	1.71	1.18	.69	.25	2.24	.0
D17S579	1.0	1.78	1.74	1.63	1.51	1.21	.82	.35	1.78	.0
D17S930	.0	.95	.94	.86	.75	.51	.28	.10	.95	.0
D17S810	.0	3.30	3.23	2.97	2.64	1.93	1.21	.50	3.30	.0
D17S791	3.0	1.14	4.75	5.00	4.72	3.78	2.61	1.30	5.02	3.9
D17S806	.0	−.50	3.11	3.44	3.27	2.58	1.74	.84	3.44	4.6
HOX2B	3.0	2.18	2.13	1.92	1.66	1.15	.65	.18	2.18	.0
D17S943	4.0	1.78	1.74	1.58	1.37	.95	.53	.18	1.78	.0
D17S788	3.0	−.07	−.07	−.08	−.09	−.10	−.08	−.05	.00	50.0
D17S787	5.0	1.90	1.87	1.73	1.55	1.14	.69	.26	1.90	.0
D17S1290	20.0	−7.22	−.70	.51	.86	.89	.59	.18	.94	14.9
D17S968		−5.06	−1.92	−1.05	−.65	−.29	−.12	−.03	.00	50.0

[a] Indicates the distance between the markers.

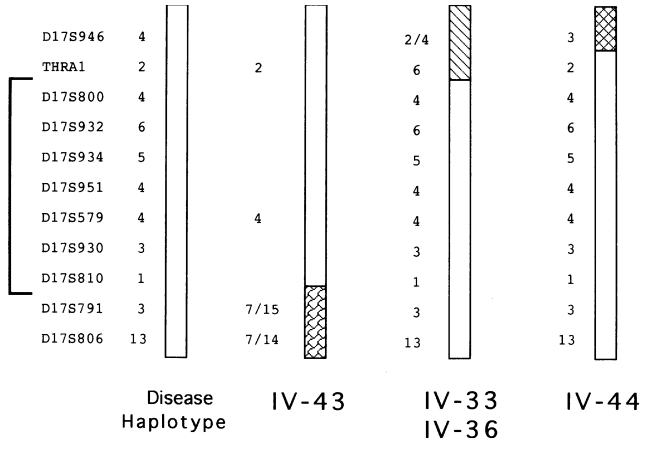

Figure 2 Recombinations defining the critical region for MSTD. Each individual is from generation IV, and the individual number refers to the pedigree shown in figure 1. Individuals IV-43 and IV-44 (brother and sister) are second cousins of individuals IV-33 and IV-36 (sisters). Individual IV-43, who is recombinant for markers D17S791 and D17S806, is a deceased affected member of the family. Diagnosis was established by neuropathological studies. Proximal recombination at markers THRA1 and D17S946 was seen in two sisters, individuals IV-33 and IV-36. Individual IV-33 is still living and was diagnosed clinically, and individual IV-36 is deceased and was diagnosed with MSTD by use of neuropathologic studies. An additional recombination with marker D17S946 was seen in individual IV-44, the deceased affected sister of individual IV-43. Individual IV-44 was diagnosed clinically and was confirmed at autopsy to have had MSTD.

region (seven markers) flanking the familial nonspecific dementia locus on chromosome 3 also were excluded as the disease locus (data not shown). Linkage to chromosome 17 was determined when two markers on the q arm showed LOD scores >3.0. The highest two-point LOD score was 5.00 with D17S791, at a distance of $\theta = 0.05$. Table 1 summarizes the two-point linkage results between the 17q markers and the disease locus. The distance between the markers is given in centimorgans, in the second column. On the basis of recombination in this family, the MSTD locus was found to be flanked by the markers THRA1 and D17S791 (fig. 2). Seven markers between THRA1 and D17S791 have been analyzed. None of the seven markers have recombination with the disease gene, and all affected individuals share the same marker haplotype, in this chromosomal region (fig. 2).

Multipoint analysis using three adjacent pairs of marker loci resulted in a maximum multilocus LOD score of 5.10, between the markers D17S932 and D17S810 (fig. 3). Not all the markers were informative; thus, the candidate region still could be reduced by examination of additional markers in this region, once they become available.

Since linkage to chromosome 17 in the region of tau was found, the open reading frame of tau was sequenced in key members of the family. Polymorphisms were

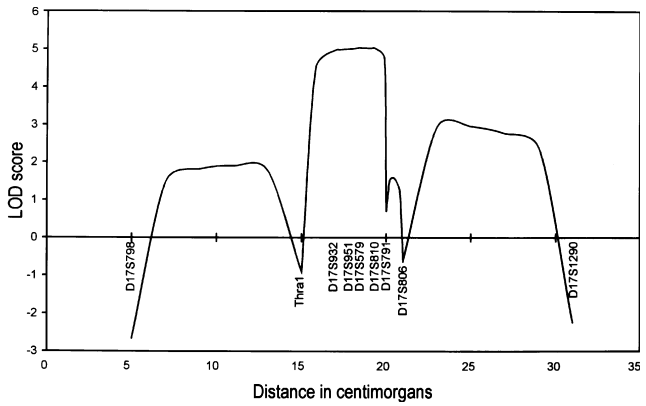

Figure 3 Results of multipoint linkage analyses between the MSTD locus and nine markers on chromosome 17q21-22. The marker names are indicated below the *X*-axis.

found within exons 7, 8, and 9. These variations in sequence also were present in a normal control.

The neuropathologic studies of a recently deceased affected member of the family showed neuronal loss in several cortical areas, the basal ganglia, the hypothalamus, the substantia nigra, and several nuclei of the brain stem. These regions also showed neuronal argentophilic, tau-immunopositive inclusions (fig. 4). Similar intracellular inclusions also were seen in oligodendroglial cells in both the gray and the white matter. The tau deposits were immunolabeled with both phosphorylation-dependent and phosphorylation-independent antitau antibodies.

Discussion

This study reports the mapping of the gene for MSTD to a 3-cM region on chromosome 17q21-22. Analysis of recombination events localized the gene between the markers THRA1 and D17S791. All affected family members have the so-called affected haplotype for markers within this region.

MSTD has a severe tauopathy in neurons and in oligodendroglia. It is interesting that the tau gene also is located in the same chromosomal region as the gene for MSTD, making it an excellent candidate gene for MSTD. The tau gene has been mapped to 17q21 by three different methods: in situ hybridization (Neve et al. 1986), radiation hybrid mapping (Abel et al. 1993), and physical mapping using YACs (CEPH-Généthon database [http://www.cephb.fr/bio/ceph-genethon-map.html]). The YACs localize tau between the markers D17S951 and D17S930.

Tau functions as a cytoskeletal protein involved in the polymerization of microtubules from soluble cytosolic tubulin. The gene for tau extends over 100 kb. Within the noncoding region of tau is a polymorphic dinucleotide repeat that has been described recently (Conrad et al. 1997). This polymorphism was analyzed through study of the MSTD family. All the affected individuals shared one allele (A3), which was to be expected, since all affected individuals have the same haplotype in the critical region. However, the marker was not very informative, with only two alleles (A0 and A3) segregating in the entire family and with nonaffected married-in individuals also carrying the A3 allele.

The tau gene has 15 exons, which are 54–753 bp in size. Intron-exon junctions have been sequenced, which would allow for sequence analysis of patient genomic DNA (Andreadis et al. 1992). All exons have been sequenced in key members of the family, and polymorphisms have been found in exons 7, 8, and 9. The promoter region and some intronic regions of tau are being examined currently.

Several other familial dementias have been localized to chromosome 17q21-22. These include PPND (Wszolek et al. 1992; Yamada et al. 1993; Wijker et al. 1996), DDPAC (Lynch et al. 1994; Wilhelmsen et al. 1994; Sima et al. 1996), familial progressive subcortical gliosis (PSG) (Lanska et al. 1994; Petersen et al. 1995), and frontal lobe dementia (FLD) (Groen and Endtz 1982) and frontotemporal dementia (FLDEM) (Yamaoka et al. 1996; Heutink et al. 1997). All of these diseases, including MSTD, are autosomal dominant neurodegenerative diseases with presenile dementia. They differ, however, in clinical and pathological presentations. FLD, DDPAC, PSG, and FLDEM individuals show behavioral and personality changes, with frontotemporal lobe atrophy (Groen and Endtz 1982; Wilhelmsen et al. 1994; Petersen et al. 1995; Yamaoka et al. 1996). Parkinsonism is seen with PPND, DDPAC, MSTD, and FLDEM (Wszolek et al. 1992; Ghetti and Farlow 1994; Lynch et al. 1994; Yamaoka et al. 1996). Abnormalities in ocular motility are exhibited with PPND, MSTD, and PSG (Wszolek et al. 1992; Ghetti and Farlow 1994; Petersen et al. 1995). Neuronal loss is severe in all these diseases, except in PSG in which the hallmark pathological feature is astrocytic proliferation in subcortical white matter (Lanska et al. 1994). None of these diseases show amyloid deposits or Lewy bodies. PPND, MSTD, and DDPAC brains show the presence of tau pathology (Yamada et al. 1993; Ghetti and Farlow 1994; Sima et al. 1996).

In spite of these phenotypic differences, it is possible that this group of diseases could be allelic, as evidenced by the mapping data. Although some of the diseases linked to this region do not show tau pathology, this fact does not necessarily eliminate this gene. However, our current gene analyses do not support tau as the disease gene. The single gene could be a gene other than tau. It is known that mutations within a specific gene can result in different clinical and pathological pheno-

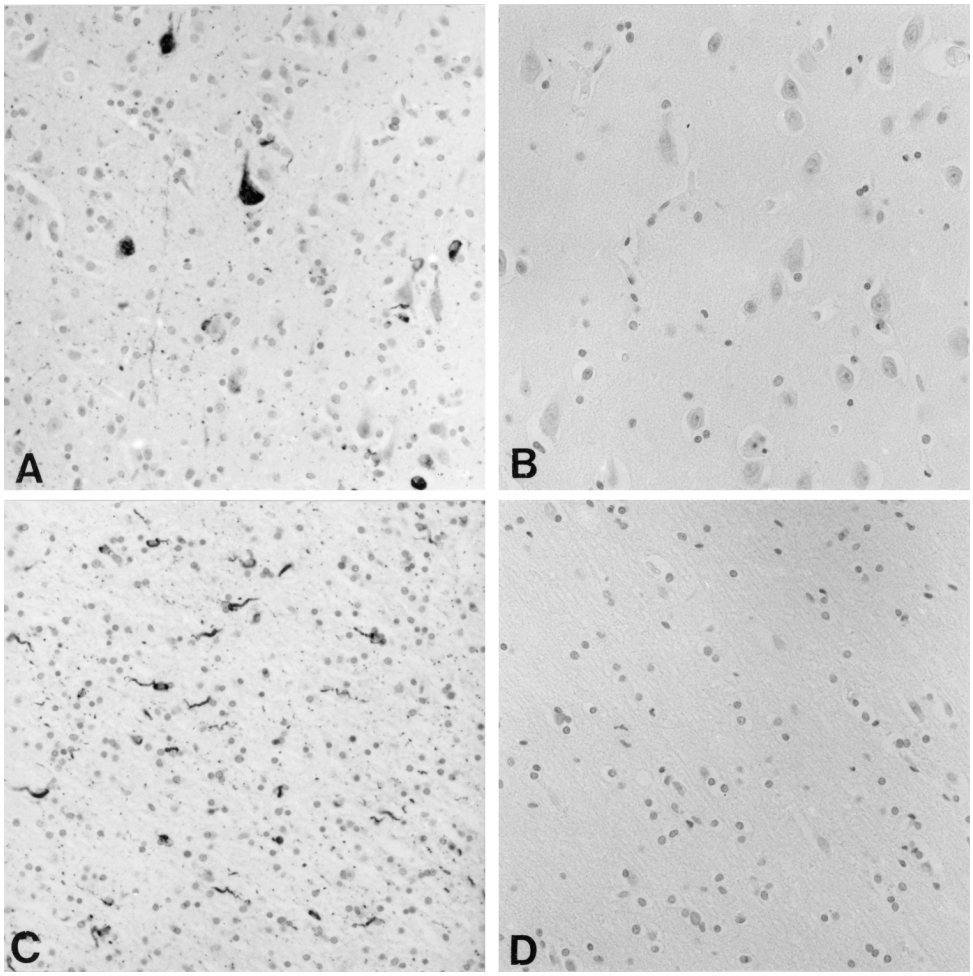

Figure 4 *A,* Cingulate cortex from an MSTD brain, showing tau-immunopositive neurons, neuropil threads, and occasional oligodendroglial cells. Immunoreactivity was seen by use of the monoclonal antibody AT8. *B,* Cingulate cortex from a normal brain, showing lack of tau immunopositivity, by use of the monoclonal antibody AT8. *C,* White matter from an MSTD brain, showing numerous tau-immunopositive oligodendroglial cells. Immunoreactivity was seen by use of the monoclonal antibody AT8. *D,* White matter from control brain, showing lack of tau immunopositivity, by use of monoclonal antibody AT8. Magnification in each panel is × 192.

typic expression in different families, as in the case of prion-associated diseases (Goldfarb et al. 1994; Ghetti et al. 1995).

Another possibility could be that there are two genes or a family of genes in this region that are responsible for these disorders. Another gene, that for glial fibrillary acidic protein, also maps to 17q21 (Bongcam-Rudloff et al. 1991) and could be a good candidate for those diseases with or without tau pathology. Tau is involved in many other neurodegenerative diseases but, so far, has not been implicated as the principle cause of any of them. Thus, it would be prudent to analyze additional candidate genes that map to the region. Several public databases list genes that map within this region. The UniGene database (http://www.ncbi.nlm.nih.gov/UniGene) (Schuler et al. 1996) lists 86 expressed-sequence tags or genes that map within D17S800 and D17S791. Of these 86, 41 are known to be expressed in the brain. The use of such databases would be a good start to the finding of additional candidate genes for MSTD.

Determination of the gene responsible for MSTD would contribute to the understanding of the etiopathogenic pathways of neuronal degeneration and eventually to the prevention of the process. Therefore, future research with the MSTD pedigree will include the analysis of other candidate genes and the testing of additional informative markers when available, in order to resolve further the location of MSTD, so that positional cloning can be pursued.

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