Brain Pathology 8: 387-402(1998)

Frontotemporal Dementia and Parkinsonism Linked to Chromosome 17: A New Group of Tauopathies

Maria Grazia Spillantini[1], Thomas D. Bird[2], and Bernardino Ghetti[3]

[1] MRC Brain Repair Centre and Department of Neurology, University of Cambridge, Forvie Site, Robinson Way, Cambridge CB2 2PY, UK.
[2] Department of Neurology, University of Washington, and Neurology 127, Seattle VA Medical Center, South Columbia Way, Seattle, WA 98108, USA.
[3] Departments of Pathology and Laboratory Medicine, Division of Neuropathology, Indiana School of Medicine, 635 Barnhill Drive, Indianapolis, IN 46202-5120, USA.

Frontotemporal dementia is a neurological disorder characterised by personality changes, deterioration of memory and executive functions as well as stereotypical behaviour. Sometimes a Parkinsonian syndrome is prominent. Several cases of frontotemporal dementia are hereditary and recently families have been identified where the disease is linked to chromosome 17q21-22. Although, there is clinical and neuropathological variability among and within families, they all consistently present a symptomathology that has led investigatores to name the disease "Frontotemporal Dementia and Parkinson-ism linked to chromosome 17." Neuropathologically, these patients present with atrophy of frontal and temporal cortex as well as of basal ganglia and substantia nigra. In the majority of cases these features are accompanied by neuronal loss, gliosis and microtubule-associated protein tau deposits which can be present in both neurones and glial cells. The distribution, structural and biochemical characteristics of the tau deposits differentiate them from those present in Alzheimer's disease, corticobasal degeneration, progressive supranuclear palsy and Pick's disease. No β-amyloid deposits are present. The clinical and neuropathological features of the disease in these families suggest that Frontotemporal Dementia and Parkinsonism linked to chromosome 17 is a distinct disorder. The presence of abundant tau deposits in the majority of these families define this disorder as a new tauopathy.

Corresponding author:
Maria Grazia Spillantini, MRC Brain Repair Centre, University of Cambridge, Forvie Site, Robinson Way, Cambridge CB2 2PY, UK; Tel.: 01223/331145; Fax: 01223/331174; E-mail: mgs11@cam.ac.uk

Neurodegenerative diseases of the brain accompanied by dementia affect 5-10% of individuals over the age of 65 in the western world and represent one of the main health related economical problem of our society. In the majority of cases, these patients suffer from Alzheimer's disease (AD). Although AD is diagnosed in life using clinical tests, the diagnosis of dementing disorders is best done post mortem on the basis of their neuropathological features. Three to 10% of cases with late-life dementia fail to show neuropathological features of AD or other common forms of non-AD dementia and they are cases described as lacking distinctive histopathology, Pick's disease without Pick bodies or frontotemporal dementia (10, 24, 34, 37, 40, 46). These cases are clinically and pathologically heterogeneous and do not constitute a distinct group. About 60% of them are hereditary (34, 39, 59). In one family the disease has been linked to chromosome 3 (9) and in 1994 Wilhelmsen et al. (74) found that the dementia in another family was linked to chromosome 17q21-22. Since then more families have been linked to the same region of chromosome 17. In October 1996, a Consensus Conference was held to identify the similarities and differences among dementias linked to that chromosome in various families, in order to establish whether they could constitute a new distinct group with comparable clinical and neuropathological features. Although clinically there is heterogeneity among and within families, the patients share frontotemporal signs and parkinsonism without resting tremor (21). Therefore, based on such similarities, these families were grouped under the name of "Frontotemporal dementia and Parkinsonism linked to chromosome 17 (FTDP-17)" (21). In some of these families the neuropathology shows intracellular tau deposits in the absence of extracellular β-amyloid deposits (21). In one of the early-studied families, the extent of tau deposition is so prominent that the disease has been named familial "multiple system tauopathy with presenile dementia" (52, 64).

In this review we intend to summarise the clinical and neuropathological features and the characteristics of tau pathology in FTDP-17, with particular emphasis on two families: Seattle family A (6, 67) and familial mul-

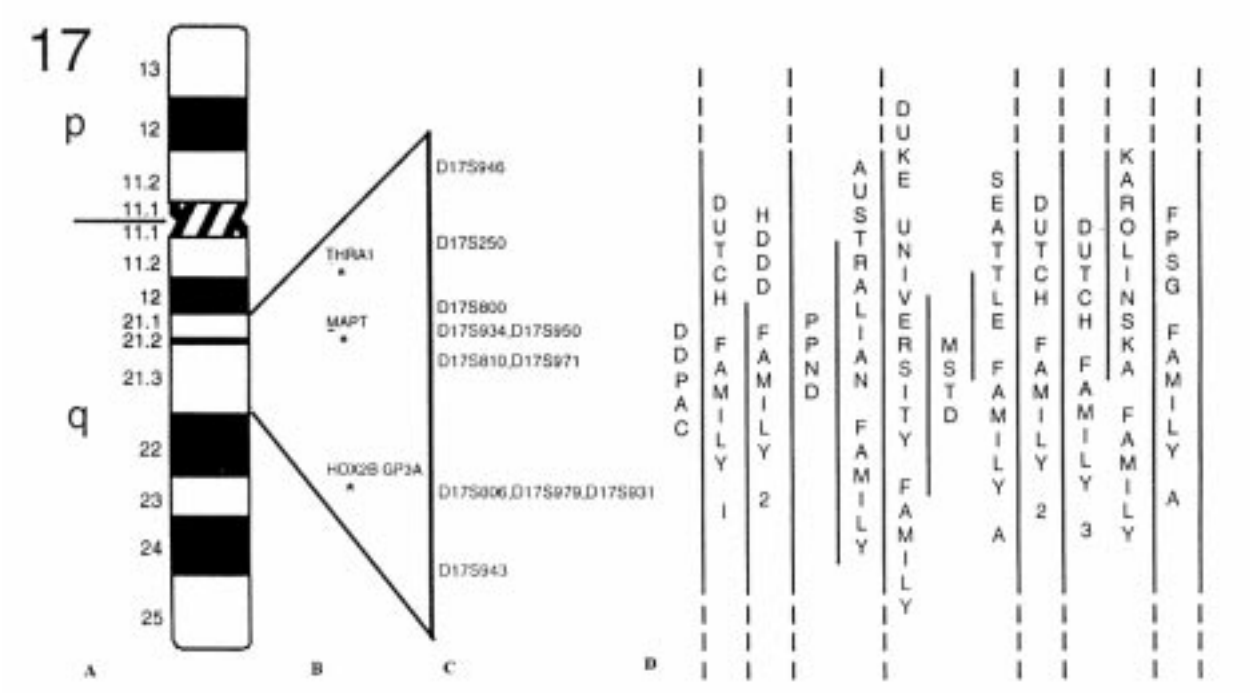

Figure 1. Linkage analysis of FTDP-17 families. The FTDP-17 locus is shown on an ideogram of a metaphase chromosome (**a**). Position of some gene loci are indicated in (**b**) while in (**c**) genetic markers are shown. Next to each family a continuous line indicates the probable location of the disease gene for that family (**d**). Dashed line indicate that the disease gene could be in a region that extends beyond the map shown in (**c**). The map is not in scale.

tiple system tauopathy with presenile dementia (MSTD) (52, 64). In both families, neuropathological and biochemical characteristics of tau have been extensively studied (63, 64, 65, 67) and they appear to represent the opposite ends of a spectrum of tau pathology observed in FTDP-17.

Families with FTDP-17.

The first familial dementia to be linked to chromosome 17q21-22 was in the Irish family Mo (74). Several members of this family have been diagnosed as suffering from schizophrenia, whereas others presented with depression, alcoholism and amyotrophy (45, 76). Most patients presented with behavioral dishinibition as an early symptom and developed successively frontal lobe dementia and parkinsonism. Based on these features the condition was named "dishinibition-dementia-parkinsonism-amyotrophy complex" (DDPAC) (45, 74). Following the description of this family, linkage of dementia to chromosome 17 was investigated in other families. In several of these, the disease was found to be linked to chromosome 17q21-22 and during the Consensus Conference it was decided that families presenting linkage with a LOD score higher than 3 should be considered as definitely linked, while families with a LOD score between 1 and 3 should be considered as probably linked (21). When the LOD score was lower than 1 the disease was considered not linked or unresolved. The dementia in eight families was definitely linked to chromosome 17q21-22, such as in the Irish family Mo also called DDPAC (45, 74), in the large family with rapidly progressive autosomal-dominant Parkinsonism and dementia with Pallido-Ponto-Nigral-Degeneration (PPND) (72, 75), in the Duke family 1684 (78), in the family with hereditary dyphasic disinhibition dementia family 2 (HDDD2) (43), in the Australian family (3, 17), in the Dutch family I previously described as a family with Pick's disease without Pick bodies (36), in MSTD (52, 64) and in the Seattle family A, also described as Seattle family BK, as familial presenile dementia with psychosis associated with cortical neurofibrillary tangles and degeneration of the amygdala or familial presenile dementia with tangles (6, 63, 67). The disease in at least one more family has now been linked to the same region of chromosome 17 (P St George Hyslop, personal communication). In five reported families the LOD score was between 1 and 3, and this was probably due to the small number of indi-

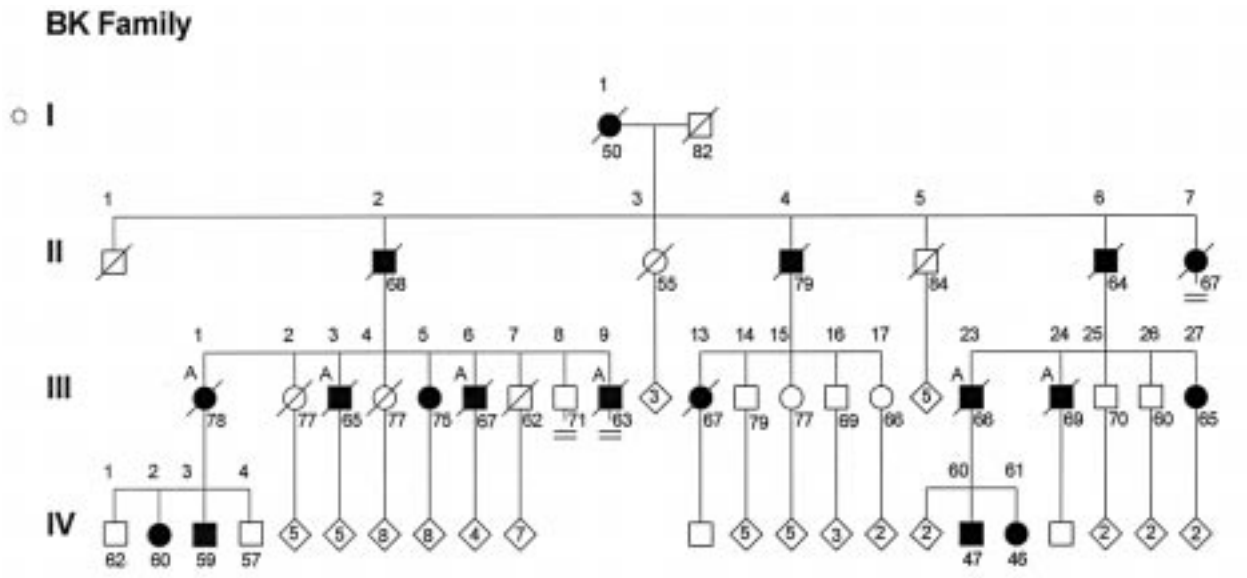

Figure 2. Pedigree of family BK/A with FTDP-17. There have been 8 affected females and 10 affected males in four generations with 6 autopsies (A above each symbol). Mean age of onset is 51.5 + 7.4 years, mean duration 13.8 + 7.8 years, and mean age at death of 66.9 + 7,0 years (6, 67).

viduals in each of these families; however, in view of clinical and neuropathological similarities with the families that are definitely linked, they were considered and defined as probably linked (21). These are the families with progressive subcortical gliosis (PSG) (42, 56), the Karolinska family (5, 23) and the Dutch families II and III (33, 36, 60).

Genetics of FTDP-17.

Several markers have been used to identify the region of linkage for the various families (21). In particular, all families definitely linked present a high LOD score for a region of about 2 cM between markers D17S791 and D17S800 which is considered to contain up to 200 genes (Figure 1) (21). In some cases, the region has been narrowed down to close to 1 Mb (52, 78). This region is close to the early-onset breast cancer gene (BRCAI) locus and several expressed sequence tags (ESTs) and genes present in it have already been identified (15, 22). The region also contains the gene encoding the microtubule-associated protein tau (1, 53) and considering that tau deposits have been reported in brains of patients in several of these families, tau is a strong candidate gene (73). A val337met change (numbering of the longest human tau isoform (25)) has been found in exon 12 of the tau gene in the Seattle A family. This change has not been found in controls, but has also not been found in any of the other FTDP-17 families. It remains to be determined if this represents a rare benign polymorphism or is in some way involved with the molecular pathogenesis of the disease in this family (P Poorkaj, GD Schellenberg and TM Bird, personal communication). Tau exons have also been sequenced in all the other families definitely and probably linked, but no mutation which segregates with the disease has been found (3, 21, 23, 36, 52, 78). Interestingly, a polymorphism in the tau gene, in the intron between exon 9 and 10, has been reported in association with progressive supranuclear palsy (PSP) (13). In FTDP-17 cases the frequency of the repeat polymorphism is not different from that in the control population. It remains to be established if other alterations in tau introns can be responsible for the development of FTDP-17. Coding regions of several other genes have also been sequenced, such as γ-tubulin (79), VAT-1 (22), DLG2 (47), VHR (38) but no mutations have been found (3). Furthermore, in these families no mutations in genes involved in familial AD, such as Amyloid Precursor Protein (APP) (68), Presenilin 1 and Presenilin 2 (35) have been found (21). Similarly, no mutation has been found in the Prion protein gene (57).

Clinical characteristics of FTDP-17.

The clinical characteristics of patients with chromosome 17 linked dementia are highly variable and wide-ranging (21). Some families can exhibit different clinical features as recently shown for DDPAC and PPND (76). This makes it difficult to recognise the disease and

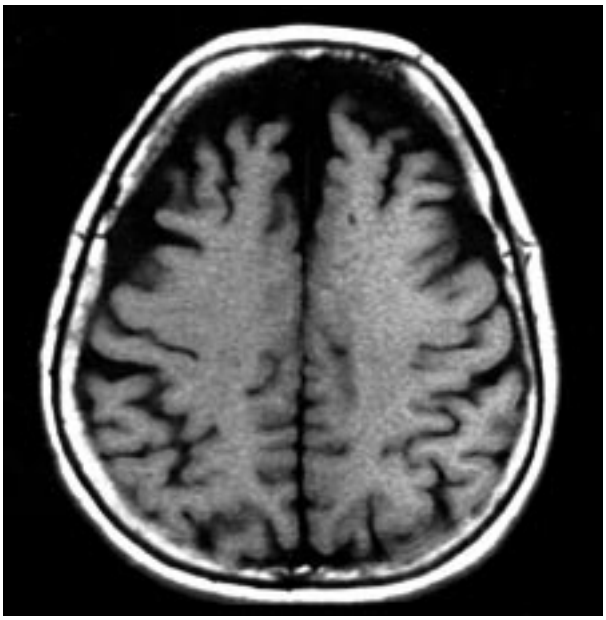

Figure 3. MRI scan. MRI of individual IV-2 in the BK/A family at the age 54 years showing bilateral frontal atrophy.

to distinguish it from other similar syndromes. However, there is a cluster of relatively common findings that allow a fairly distinct picture to be drawn that aids in the identification of this unusual disorder. The clinical description is based on 10 published definitely and probably linked families with this disease and has been summarized by Foster et al. (21).

The first symptoms usually begin in the 5th decade of life, but have occurred from the 3rd to 6th decades in some patients. There is often a positive family history of a similar syndrome occurring in multiple family members, as shown in Figure 2 for Seattle family A . At the present time the disease is defined as an autosomal dominant condition. The symptoms and signs are insidious in onset and slowly progressive over many years. The total disease duration is usually 10-12 years, with a range of 3-30 years. The symptoms and signs can be divided into behavioral, cognitive and motor phenomena.

Behavioral disturbances are frequently the initial symptoms. There is often dishinibiton associated with inappropriate behavior and poor impulse control. The patients may be apathetic, socially withdrawn and neglectful of personal hygiene. There may be repetitive and compulsive behavior. Prominent psychosis similar to schizophrenia has occurred including auditory hallucination, delusion and paranoia. Verbal and physical aggression may occur and alcoholism has been reported (21). Patients have been arrested and jailed or placed in psychiatric hospitals. Judgement is impaired and may be apparent in poor handling of finances. There may be hyperorality and hyperphagia for both food and non-food objects. In all families, but in particular in the Seattle family A, some of the patients have been diagnosed with psychiatric disorders (6, 67).

Cognitive impairment is primarily in the realm of executive function. There are deficits in judgment, planning and reasoning. There is frequently a surprisingly good preservation of memory, orientation and visuospatial functions. Some individuals experience language difficulties that include dysnomia and aphasia. Later in the disease (often several years later) a more typical dementia appears with deficits in memory, orientation and visuospatial functions, sometimes ending in mutism.

Motor disturbances are common, but often not noted in the early stages of the disease. Bradykinesia with axial and limb rigidity and postural instability may occur and mimics a Parkinsonian syndrome which is clearly evident in PPND (21, 75, 76). However, resting tremor is uncommon and there is rarely a response to L-dopa. Some patients have had upper motor neuron signs, including brisk tendon reflexes and a Babinski sign (21). Less common, but occasionally reported motor findings have included muscle weakness and wasting with fasciculation, myoclonus, action tremor, slow oculomotor saccades, dysphagia, dysarthria and impairment of up-gaze (3, 5, 6, 17, 21, 36, 42, 45, 64, 67, 75, 76, 78).

Initial EEG and CT or MRI imaging studies may be normal (14, 21). Later in the disease there may be focal atrophy, often of the frontal areas (as shown in Figure 3 for Seattle family A) and sometimes the atrophy is asymmetrical. There may be evidence of hypoprofusion or hypometabolism of the frontotemporal areas and reduced striatal uptake of 6 fluoro-L-dopa (21, 75, 76).

In summary, the typical patient with chromosome 17-linked dementia develops abnormal, disinhibited behavior in the 5th decade without impairment of memory or orientation which progressively worsens over several years and is eventually associated with severe dementia, bradykinesia, rigidity and evidence of frontal and/or temporal atrophy. This occurs in the context of other family members with a similar history. The early preservation of memory and orientation is different from AD (21). The early severe behavioral changes combined with lack of resting tremor and absence of response to L-dopa distinguish this syndrome from Parkinson's disease. The usual preservation of eye movements, in most patients, especially of down-gaze and horizontal gaze, and the positive family history help to distinguish it

from PSP. Patients with FTDP-17 have not been noted to experience the alien hand syndrome which is common in cortico basal degeneration (CBD). The rapidly fluctuating mental status and extreme sensitivity to neuroleptic drugs associated with diffuse Lewy body disease have not been reported in FTDP-17 subjects. Thus, a slowly but relentlessly progressive, familial, frontotemporal dementia syndrome is the hallmark of this disorder, although the myriad of associated signs and symptoms and the lack of a specific diagnostic test make for a complex differential diagnosis.

Neuropathology of FTDP-17.

In chromosome 17 linked dementia atrophy is consistently found in the frontal and temporal cortices, basal ganglia and substantia nigra (21). Neuronal loss and some rarefaction of the superficial cortical layers are consistently observed along with gliosis of gray and white matter. Cell loss is less severe in the hippocampus. Among subcortical regions, there is moderate to severe atrophy of the caudate and putamen, severe atrophy of the amygdala (Figure 4, Seattle family A) and of the hypothalamus. Cell loss is consistently found in the substantia nigra and less consistently in other midbrain, pontine and medullary nuclei. Motor neuron loss in the spinal cord has been reported only in some cases. Lewy bodies, amyloid deposition and Pick bodies are not found in the families reported so far (21).

In patients from some chromosome 17 linked dementia families, argentophilic intraneuronal inclusions have been reported in neocortex, basal ganglia, hypothalamus, midbrain, pons, medulla, and spinal cord. These inclusions correlate with tau immunopositivity (21). Argentophilic intracytoplasmic and tau immunopositive inclusions in glial cells have also been reported in patients of some families, including the MSTD (64, 65), DDPAC (62), Duke family 1684 (66), PSG (56) and PPND (77). Since immunohistochemistry for tau has not been systematically carried out, it remains to be determined whether intraneuronal and glial tau pathology are consistent features of FDTP-17. The most detailed neuropathological studies have been reported for the DDPAC (62) and Seattle family A (67).

Concerning the neuropathological features of MSTD most data are related to the intermediate and late stage of the disease. We have little or no information on the neuropathology of the early stage. In the intermediate stage of MSTD (6 years from the onset of symptoms) there is mild atrophy of the cerebrum, even though the characteristic histopathological changes in the cortex, subcortical regions and white matter are already prominent. There may be mild atrophy of the caudate nucleus and a considerable reduction of the pigmentation of the substantia nigra and locus coeruleus.

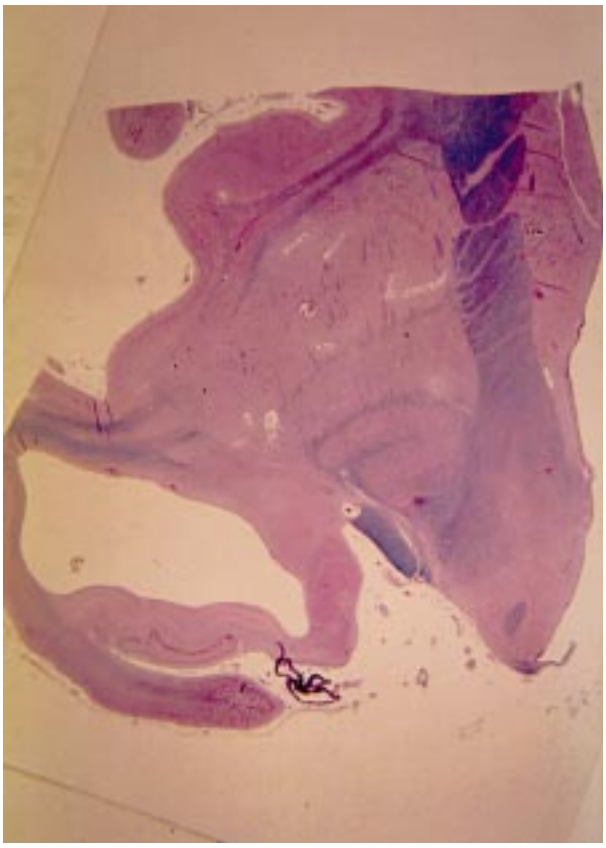

Figure 4. Atrophy of the amygdala in a Seattle family BK/A patient. Section through the striatum of case III-3 demonstrating severe atrophy of the amygdala. The patient died at age 78 after 26 years of symptoms. (Luxol fast blue-periodic acid-Schiff reaction-hamatoxylin, x1.6; courtesy S.M. Sumi).

Most neuropathological data are from MSTD patients in the late stages of the disease, between 12 and 20 years from the onset of symptoms. In the late stages, the brain is severely atrophic, ranging in weight from 935 to 1,120 gms. Atrophy involves the frontal and temporal lobes, as well as the cingulate gyrus, while the parietal lobes are involved to a lesser extent. All frontal gyri including those of the orbital surface are affected. In the temporal lobe, the atrophy is most severe in its rostral part and the superior temporal gyrus appears most affected. Atrophy of the caudate nucleus, putamen, globus pallidus, amygdala, and ventral hypothalamus is evident, while the hippocampus and thalamus appear relatively spared on gross examination. The lateral ventricles are dilated throughout their subdivisions. The white matter of the centrum semiovale and of the corpus

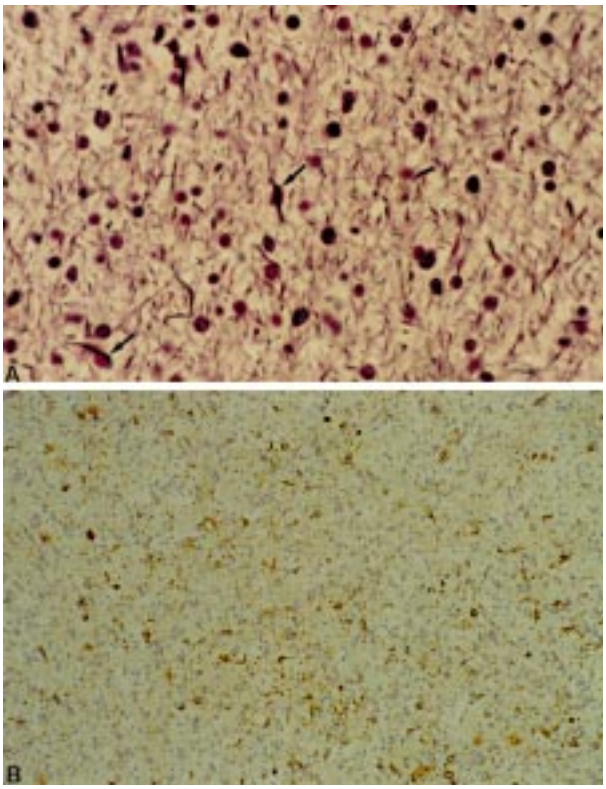

Figure 5. Glial cytoplasmic inclusions in white matter from a MSTD patient. **A.** White matter from a MSTD patient. Argentophilic intracytoplasmic inclusions (arrows) are seen in glial cells. Bodian stain. X 688. **B.** White matter from a MSTD patient showing numerous tau immunopositive glial cells. Immunohistochemistry with AT8 antibody. X 96.

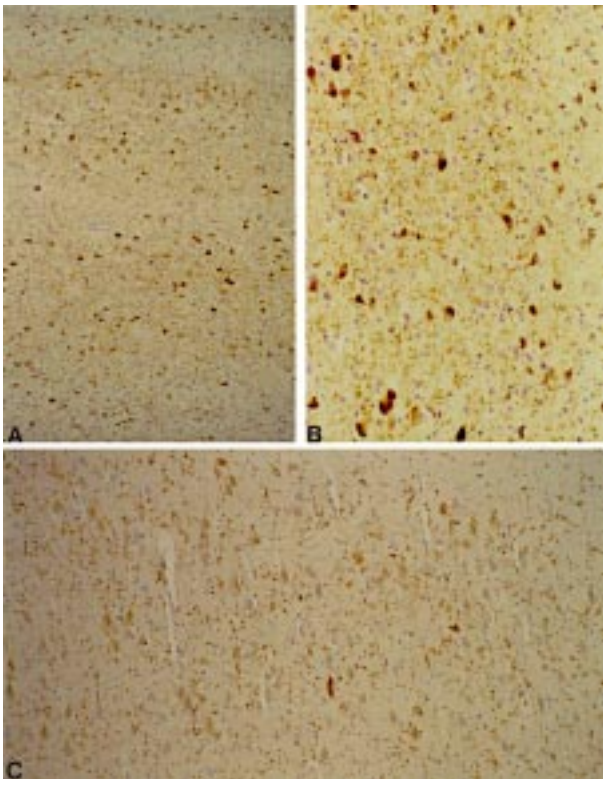

Figure 6. Tau immunostaining in cerebral cortex and hippocampus of an MSTD patient. **A.** Cerebral cortex from a MSTD patient. Nerve cells and neuropil of multiple layers show tau deposits. Immunohistochemistry with phosphorylation dependent anti-tau monoclonal antibody AT8, which recognizes tau phosphorylated at Ser-202. and THR20 X 47. **B.** Cerebral cortex from a MSTD patient shows numerous nerve cells with intracytoplasmic tau deposits and tau immunopositive neuropil threads. Immunohistochemistry with AT8 antibody. X 115. **C.** Hippocampus from a MSTD patient. Pyramidal neurons show mild tau immunopositivity while neuropil threads show strong immunopositivity. Immunohistochemistry with AT8 antibody. X 54.

callosum as well as that of the temporal lobes is substantially reduced in bulk. The substantia nigra and the locus coeruleus show a marked reduction in pigmentation. In some instances, mild atrophy of the cerebellar cortex as well as discoloration and atrophy of the dentate nucleus may be observed. The pons may be reduced in bulk.

Concerning the microscopical features of MSTD the severity of histopathological changes varies from patient to patient; however, there is uniformity in the distribution of lesions. The alterations are conspicuous in both gray and white matter. In the most affected cortical areas, the cortex shows neuronal cell loss and gliosis throughout its thickness. The atrophy of the cortical layers is associated with a severe rarefaction of the neuropil, particularly at the level of the upper two layers. Severe astrogliosis is present. Bodian stain reveals the presence of argyrophilic cytoplasmic inclusions in neurons and oligodendroglia (Figure 5). The latter are present in both gray and white matter areas. The hippocampal formation is relatively spared with mild neuronal loss in Ammon's horn and the subiculum. In some patients, large numbers of Hirano bodies may be found in pyramidal neurons.

Of the subcortical structures, nerve cell loss and gliosis are prominent in the caudate nucleus, putamen, globus pallidus, amygdala and hypothalamus. The substantia nigra, locus coeruleus, periaqueductal gray, third and fourth cranial nerve nuclei, reticular nuclei, raphe neurons, and dorsal nucleus of the vagus nerve are all significantly affected by neuronal loss. Argentophilic inclusions in neurons and oligodendroglial cells are present also in these regions, with different degree of severity.

Neurofibrillary tangles can be seen in hypothalamus,

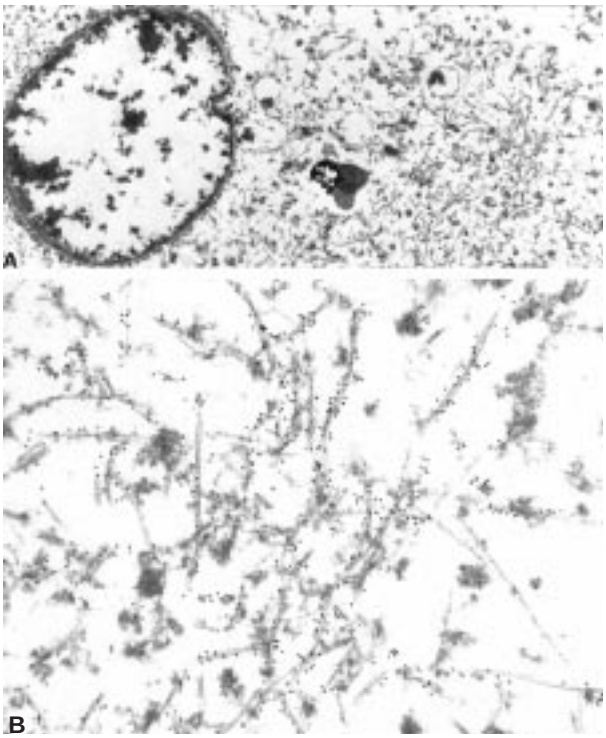

Figure 7. Electron micrographs of neuronal cytoplasmic inclusions in cerebral cortex of a MSTD patient. **A.** Nerve cell perikaryon from the cerebral cortex of a MSTD patient. Multiple filamentous structures are seen in the cytoplasm. Electron microscopy, X 6,600. **B.** Intracytoplasmic filaments from nerve cell shown above. Many filaments show a characteristic periodicity and are decorated with gold particles. Immunogold cytochemistry using phosphorylation dependent anti-tau monoclonal antibody PHF1, which recognizes tau phosphorylated at Ser-396 and Ser-404.

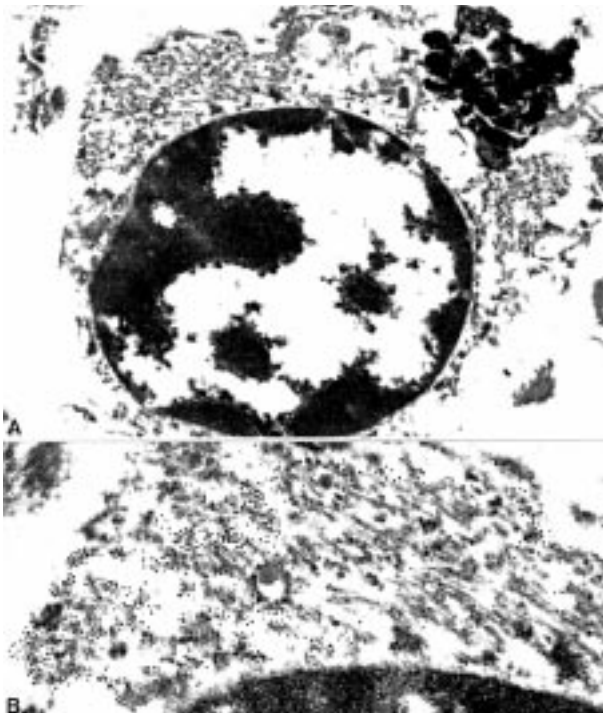

Figure 8. Electron micrographs of glial intracytoplasmic inclusions in a MSTD patient. **A.** Glial cell from a MSTD patient. The cytoplasm contains filamentous aggregates. Electron microscopy, X 12,000. **B.** Intracytoplasmic filaments from glial cell shown above. Many filaments are decorated with gold particles. Immunogold cytochemistry using antibody PHF1. X 32,500.

midbrain nuclei with particular severity in the periaqueductal gray matter, and in several pontine nuclei. In the cerebellum, loss of Purkinje cells may be present.

The cerebral white matter shows gliosis and presence of numerous intracytoplasmic oligodendroglial argentophilic inclusions, particularly numerous in the frontal and temporal white matter regions.

In the spinal cord, axonal swellings and a mild loss of nerve cells are present in the anterior horn and dorsal gray matter. Loss of nerve fibers in the propriospinal tract, as well as in ventral and lateral spinothalamic tracts and in the lateral vestibulospinal tract may be observed in myelin preparations.

Immunohistochemical studies reveal numerous intracytoplasmic tau-positive inclusions in frontal, temporal, insular and cingulate cortex as well as in hippocampal formation, subcortical nuclei, brainstem nuclei and spinal cord gray matter (Figure 6) (64, 65). Tau-positive deposits are present not only in nerve cells, but also in large numbers of glial cells, chiefly oligodendrocytes, as identified by their characteristic size and morphology (Figure 5). Some astrocytes, identified by glial fibrillary acidic protein staining, are also tau-immunoreactive; no astrocytic plaques are observed in either paraffin or vibratome-cut tissue sections. The tau-positive lesions in neurons and glial cells also are stained by the anti-heparan sulfate antibody 10E4 (29, 64). No Aβ staining has been observed in any of the tissues examined. Many of the tau-positive structures are also ubiquitin-immunoreactive. No immunohistochemical staining has been detected using multiple antibodies to the prion protein.

By electron microscopy, cortical neurons contain cytoplasmic filaments reminiscent of the paired helical filaments (PHFs) found in AD (16), but with a different diameter and periodicity (Figures 7) (64, 65). These filaments are loosely distributed in the cytoplasm. In one patient, these filaments co-exist with bundles of paired helical filaments indistinguishable from those observed in AD. By immunoelectron microscopy both types of

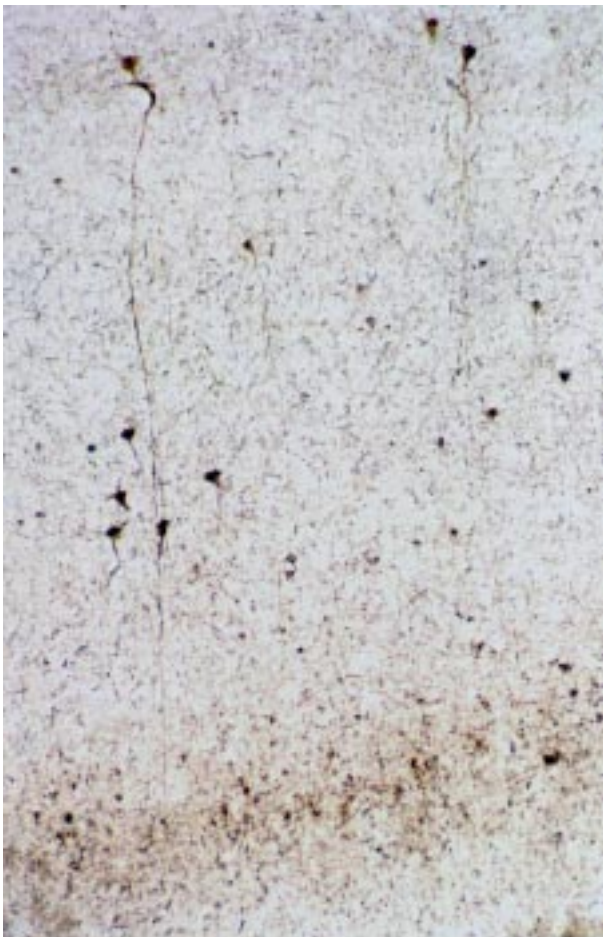

Figure 9. Tau staining in cerebral cortex of a Seattle family A patient. Double staining using anti-tau antibodies AT8 (brown) and PHF1 (blue). The majority of neurofibrillary tangles and neuropil threads, in different layers of the cerebral cortex, are double stained. Some structures are stained only by AT8. X 50

filaments are decorated by anti-tau antibodies (Figures 7, 8).

Inclusions of a similar type have been studied by electron microscopy in neurons of midbrain nuclei. Such neurons are found to contain tangles of filamentous structures with tubules measuring 15-20 nm in diameter. The periodicity of such filaments could not be clearly determined. Numerous oligodendroglial cells also contain bundles of tightly packed filaments for which a periodicity could not be clearly demonstrated (Figure 8).

The pathological and cytological changes of MSTD are distinct. However, there is some overlap with the changes observed in PSP and CBD, although, the clinical features of these disorders are quite distinct. MSTD differs from PSP by the severe involvement of the frontal, insular, temporal and cingulate cortices, by the atrophy of numerous subcortical gray matter regions and by the severity of the oligodendroglial inclusions. CBD starts at a later age than MSTD and progresses more rapidly. In CBD, there is frontal and parietal atrophy with relative sparing of the temporal lobe. Among the subcortical structures, the caudate nucleus, putamen, globus pallidus, and the substantia nigra may be involved. However, the extent and severity of tau immunoreactivity in the cortex and subcortical nuclei as well as in the midbrain, pons, medulla, and spinal cord nuclei appear to be unique of MSTD.

Tau pathology in FTDP-17.

The presence of tau deposits in some FTDP-17 families has been recognised before the study linking the disorder to chromosome 17q21-22. In 1992 Sumi et al. (67) described neurofibrillary tangles (NFTs) in neurones in neocortex, amygdala and parahippocampal gyrus in Seattle family A. In this family tau pathology was further investigated by immunohistochemistry, biochemistry and electron microscopy (63), the same techniques which were later used to investigate the characteristics of tau deposits in neurones and glial cells in MSTD (64, 65). In 1993 Yamada et al. described tau deposits in PPND (77) and these have also been reported in neurons and glial cells in DDPAC (62), progressive subcortical gliosis (56) and more recently in the Australian family (3). However, no tau inclusions were reported in the Dutch families (36), Duke family 1684 (78), the HDDD2 family (21) and the Karolinska family (5, 23). More recently, using immunohistochemistry as well as biochemistry and electron microscopy tau deposits have been found in the Duke family 1684 (66), in the HDDD2 family (CL Lendon et al, (1998) Neurol in press; MG Spillantini, C Lendon, T Lynch, DW McKeel, unpublished observation) and studies using phosphorylation dependent and independent anti-tau antibodies are in progress in the Dutch families (MG Spillantini, JC Van Swieten, manuscript in preparation). The Karolinska family is now the only one where tau pathology has not been found (5, 23). Based on the characteristics of tau pathology the families with dementia linked to chromosome 17 are more similar to Seattle family A or to familial MSTD. The diseases in these two families appear to represent the opposite ends of tau pathology in FTDP-17.

In Seattle family A phosphorylation-dependent and phosphorylation-independent anti-tau antibodies stain numerous NFTs in neocortex, amygdala and parahippocampal gyrus, but not in the hippocampus proper,

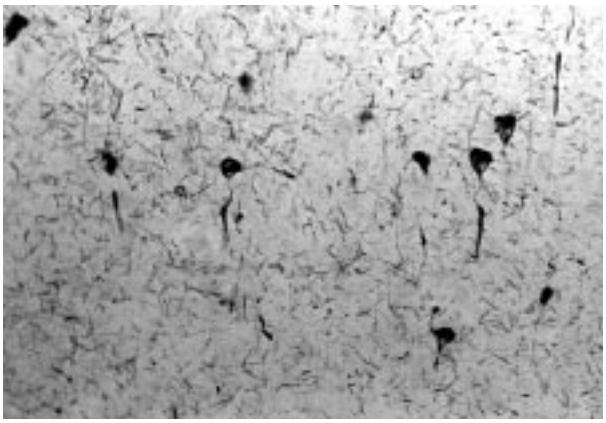

Figure 10. Neurofibrillary tangles in cerebral cortex of a patient from Seattle family A. Neurofibrillary tangles and neuropil threads are stained by anti-tau antibody PHF1 in cerebral cortex of a Seattle family A patient. Tau staining is present in cell soma and apical dendrites. X 85.

where neuronal loss and gliosis are only found in CA1 (67). In neocortex anti-tau antibodies often stain cells in a pre-tangle stage, as well as intracellular tangles and neuropil threads (NTs) (Figure 9). Neuritic plaques are absent. In neocortex NTs are distributed homogeneously between layers II and V, with smaller numbers in layer I (Figure 9), while NFTs are mainly present in layers II, III and V (Figure 9). Tau deposits are only present in neurons and no specific tau staining has been observed in glial cells. In NFTs tau deposits are present in the cell soma and, like in AD, they often extend into the apical dendrite (Figure 10), but unlike AD, β-amyloid deposits and neuritic plaques are missing (63, 67).

In familial MSTD tau deposits have been found in neocortex, hippocampal formation, substantia nigra and numerous brainstem nuclei, and spinal cord (64, 65). These deposits are stained by phosphorylation-dependent and phosphorylation-independent anti-tau antibodies and they are present in cell bodies and in neurites as NFTs and NTs (Figures 5, 6) (64, 65). As in Seattle family A NPs and ß-amyloid deposits are not found. NFTs are mainly in a pre-tangle stage and as in other FTDP-17 families, appear globose and not flame-shaped as in AD (Figure 11), and they are usually confined to the cell soma. Furthermore, tau deposits are present in both neurones and glial cells, mainly oligodendrocytes (Figures 5, 6). Tau deposits in oligodendrocytes have also been reported in PPND (77), DDPAC (62), Duke family 1684 (66) and PSG (56). In MSTD granule-like structures, associated with neuronal and glial cell bodies are also stained by some anti-tau antibodies (Figure 12) (64, 65).

NFTs and NTs in Seattle family A contain filaments

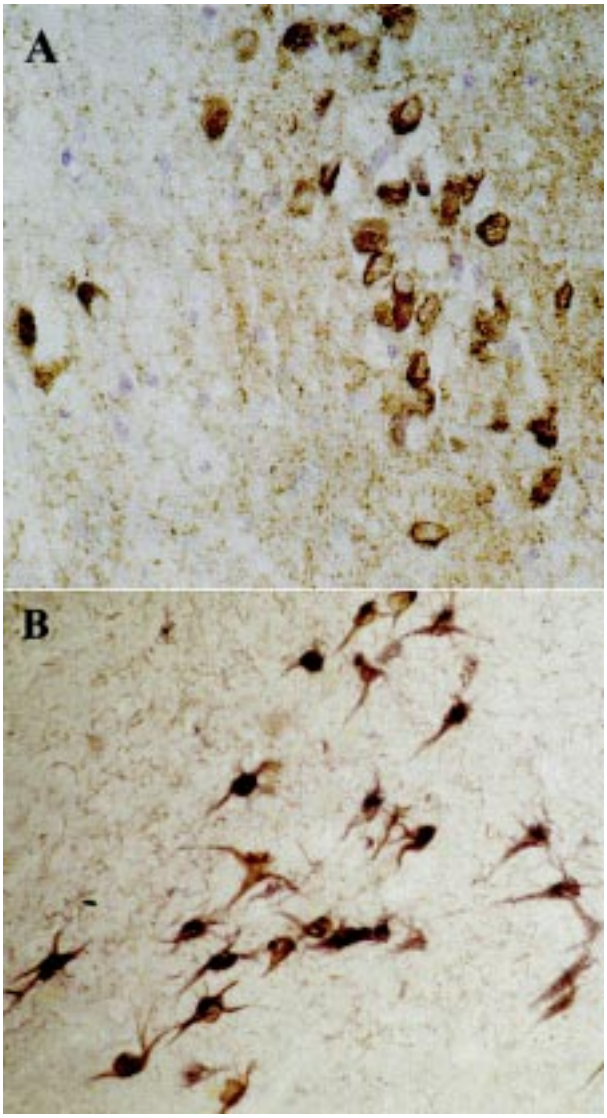

Figure 11. Tau staining in stellate cells in layer II of entorhinal cortex. AT8 staining of stellate cells in layer II of entorhinal cortex in brains of patients with (A) MSTD like pathology and (B) Alzheimer's disease. Neurofibrillary tangles appear globose in (A) and "flame-shaped" in (B). X 125

identical to AD PHFs (Figures 13, 14) with a diameter of 11-20 nm and a periodicity of 80 nm (63, 67). These PHFs are visible at the electron microscope in both tissue sections (Figure 13) (67) and in dispersed filaments preparations (63) (Figure 14). They are immunogold labelled by anti-tau antibodies (63). By contrast, in MSTD filaments appear as slender twisted ribbons of 6-22 nm in diameter and a variable 140-300 nm periodicity (Figure 14) (64). These filaments are observed by electron microscopy in both neurones and glial cells

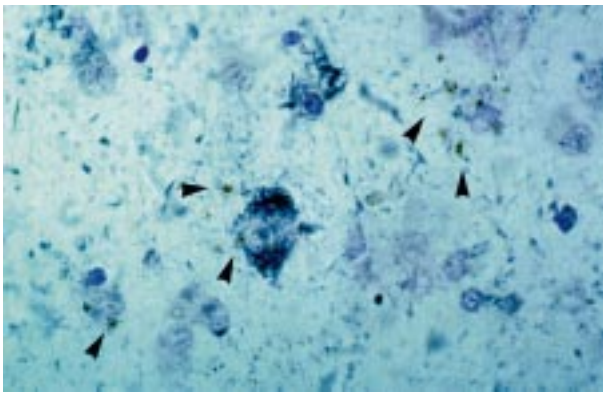

Figure 12. Double staining of temporal cortex from a MSTD patient with anti-tau antibodies 12E8 (brown) and AT8 (blue). 12E8 and AT8 recognise respectively phosphorylated Ser 262 and/or Ser-356 and Ser 202 and Thr 205 of the longest human tau isoform (25). Arrows indicate granular structures stained by 12E8. Blue fibrillary deposits are stained by AT8. X 250.

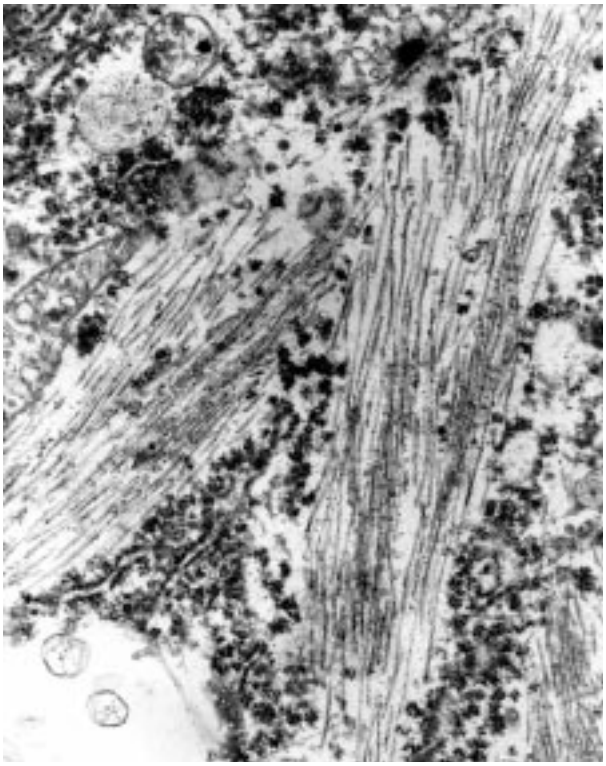

Figure 13. Paired helical filaments in a brain from a subject from Seattle family BK/A. Electron micrograph of paired helical filaments from neurofibrillary tangles in the brain of subject III-6 in family BK/A who died at age 67. (EM X17,843; courtesy D. Nochlin).

(Figures 7, 8) and are immunogold labelled by anti-tau antibodies both in tissue sections and in dispersed filament preparations (Figure 7, 8) (64). Similar filaments have been observed in the Duke family 1684 (66). They differ from AD PHFs, Seattle family A PHF-like filaments and PSP and Pick's disease straight filaments (Figure 14) (20, 65) but present some similarities with tau filaments from CBD (41, 69).

By immunoblotting sarkosyl-insoluble tau extracted from the brain of a patient of Seattle family A appears as 3 major bands of 60, 64 and 68 kDa and a minor band of 72 kDa, exactly like in PHF-tau from AD (28, 30, 44, 63). When this preparation is treated with alkaline phosphatase at high temperature the 4 bands resolve into 6 bands which align with the recombinant tau isoforms, indicating that, as in AD, these filaments contain all tau isoforms (25, 28, 31, 44, 51). Furthermore, the relative amount of tau isoforms parallels that in control brain, with tau isoforms with 3 repeats being more abundant than tau isoforms with 4 repeats (27, 28).

Sarkosyl-insoluble tau from MSTD appears on immunoblots as 2 major bands of 64 and 68 kDa and a minor band of 72 kDa (64). A similar pattern is observed in the Duke family 1684 (66). After alkaline phosphatase treatment at high temperature these bands resolve into 2 major bands which align with recombinant tau isoforms with 4 repeats and 0 and 29 amino-terminal amino acids inserts (Figure 15) (64). A minor band which aligns with the longest human brain tau isoform with the 58 amino acid amino-terminal insert and 4 repeats can also be visible. This indicates that filaments in MSTD contain mainly tau isoforms with 4 repeats (25, 26). In the Seattle family A and in MSTD, soluble tau extracted by perchloric acid (27) appears as a set of 6 bands which align with recombinant tau isoforms. In the Seattle family A the relative abundance of tau isoforms with 3 and 4 repeats is similar to that seen in control brains. By contrast, in MSTD a difference in the amount of soluble tau with 3 and 4 repeats is present, in that a relative preponderance of tau isoforms with 4 repeats is observed (MG Spillantini, unpublished observation).

In one out of 9 patients with MSTD, filaments typical of MSTD and AD like PHFs coexist and tangles have a distinct shape, suggesting an overlap of two pathologies. Interestingly, this patient presents 3 major sarkosyl-insoluble tau bands of 60, 64 and 68 kDa and a minor band of 72 kDa, as observed in AD and in Seattle family A. However, in this patient the difference in the relative amounts of tau isoforms with 3 and 4 repeats, in soluble tau, is present, similarly to the other affected

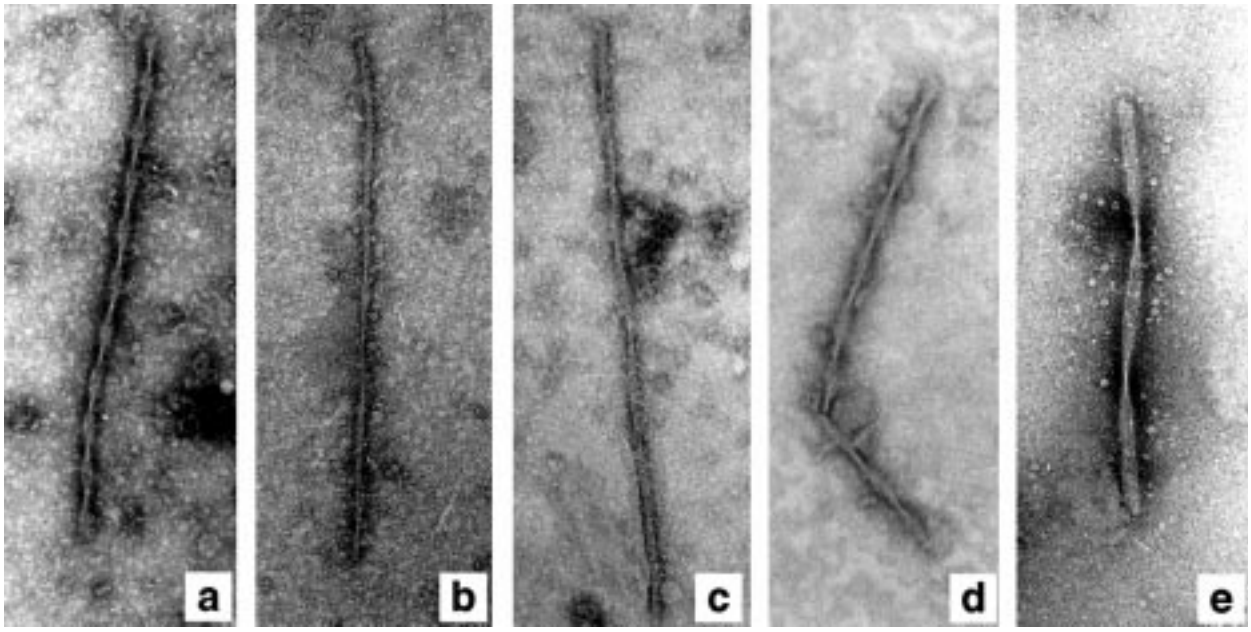

Figure 14. Electron micrographs of tau containing-filaments from AD (**a**), PSP (**b**), Pick's disease (**c**), Seattle family BK/A (**d**) and MSTD (**e**). Filaments from MSTD (**e**) have a different morphology from filaments from AD, PSP, Pick's disease and Seattle family A. Filaments in AD (**a**) and Seattle family A (**d**) appear similar. X 55,000.

members of the MSTD family.

In summary, tau pathology appears in Seattle family A as NFTs and NTs. These deposits are found mainly in neurones and they contain filaments indistinguishable from AD PHFs and SFs (Figures 12, 13) (63, 67). Tau contained in these filaments appears on immunoblots as major bands of 60, 64, 68 kDa and a minor band of 72 kDa. These bands contain all 6 tau isoforms. Soluble tau appears as 6 bands which are similar to tau extracted from normal brain. Despite the ultrastructural and biochemical similarities of tau deposits to those of AD, tau pathology of the Seattle family A differs from that present in AD by the regional and cellular distribution of NFTs and NTs and by the absence of NPs (63, 67).

In MSTD tau contained in filaments appears on immunoblots as 2 major bands of 64 and 68 kDa and a minor band of 72 kDa and these bands contain mainly tau isoforms with 4 repeats. Soluble tau from MSTD brain appears as 6 bands, but the ratio between tau isoforms with 3 and 4 repeats is altered compared to control brain. In MSTD, filaments contain tau which appears as 2 bands of 64 and 68 kDa and a minor band of 72 kDa, similar to what is seen in PSP (20, 61) and CBD (19, 41). However, MSTD filaments differ from those present in PSP (Figure 14). In general the tau pathology is more diffuse in MSTD as compared to PSP. In MSTD and CBD filaments appear ultrastructurally similar and in both cases they contain 2 major tau bands of 64 and 68 kDa and a minor band of 72 kDa (19, 41, 64, 65). However, no astrocytic plaques typical of CBD (11, 19) have been observed in MSTD and, while tau isoforms with 4 repeats appear to be the major isoforms in MSTD filaments, these tau isoforms have been reported not to be present in CBD (41). Tau deposits in MSTD are stained by an anti-tau antibody which recognises tau exon 3 (64), while lack of staining with similar antibodies has been reported in CBD (19, 41, 54). Most families with FTDP-17, where tau pathology has been investigated, present a pattern closer to MSTD than to Seattle family A.

Outlook

Clinical and neuropathological features indicate FTDP-17 as a distinct neurodegenerative disease. Tau pathology in neurons and glia, accompanied by nerve cell loss and gliosis, are the main neuropathological features in most patients with FTDP-17. At this time, while the genetic defect of the disease remains to be discovered, the relationships between clinical symptoms and neuropathological features are only partially understood. Clinical and behavioural neurology, neuropsychology as well as brain imaging studies, such as positron emission tomography and functional magnetic resonance are needed in order to characterize the functional alterations of the early stages, the neurologic deficits seen in the intermediate stages and the profound

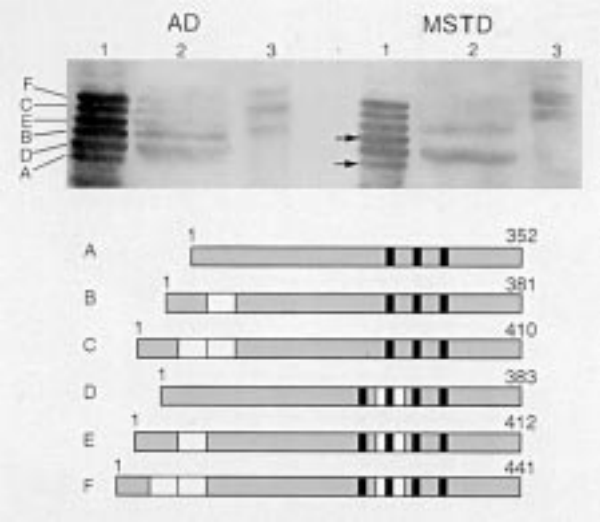

Figure 15. Immunoblots of sarkosyl-insoluble tau from cerebral cortex of AD and MSTD patients. Immunoblots represent sarkosyl-insoluble tau (PHF-tau) before (lane 3) and after (lane 2) alkaline phosphatase treatment using anti-tau antiserum BR133, raised against the peptide 1-16 of human tau (25). In AD the 60, 64, 68 and 72 kDa bands align with recombinant tau isoforms (lane 1) after alkaline phosphatase treatment while in MSTD the 64, 68 and 72 kDa bands resolve, after alkaline phosphatase treatment, into 2 major bands which align with recombinant tau isoforms (lane 1) of 383 and 412 amino acids (isoforms D and E in the schematic diagram). Arrows indicate the position of the usually abundant 3 repeats tau isoforms, which, after alkaline phosphatase treatment of sarkosyl-insoluble tau (lane 2), are not present in MSTD.

dementia of the late stages of FTDP-17. Such studies should be correlated with a biochemical analysis of tau protein in cerebrospinal fluid during life and in brain tissue post mortem. Thus, it will be possible to determine to which extent clinical signs at various stages of the disease may be correlated with tau pathology in neurons and oligodendroglia, as well as neuronal degeneration and nerve cell loss, as previously done in AD (2, 7). We may suggest that functional alterations of the neuronal network, caused by the tauopathy, may be correlated with some of the psychiatric and neurologic symptoms seen during the earliest stages of the disease, whereas, subsequently, degeneration of neuronal processes, loss of synapses and nerve cell perikarya, secondary to the tauopathy most likely constitute the anatomical substrate of the progressive neurologic deficit and the dementia. Similar to the investigations carried out in Alzheimer's disease and in other degenerative dementias with a complex pathogenesis, defining the clinical and the pathological stages of FTDP-17 and dissecting the molecular pathways of the tauopathy may lead to novel insights into the role of tau in neurodegeneration.

Currently, in addition to FTDP-17, forms of sporadic frontotemporal dementia have been reported (37, 46). Furthermore, several sporadic cases of dementia characterised by tangles without concomitant amyloid deposits, have been described (4, 24, 70) and in some cases they often show clinical and/or neuropathological similarities to the disease in FTDP-17 families (24, 40, 48, 70). It remains to be determined if any of these sporadic cases may, on a closer inspection, turn out to be familial. Interestingly, although the majority of cases described as sporadic frontotemporal dementia do not show tau deposits (10, 37, 46) in a few patients hyperphosphorylated tau bands have been recently detected biochemically (71), it remains to be seen if these are sporadic cases of typical frontotemporal dementia or cases of sporadic dementia with only tangles.

When the gene carrying the mutation that causes FTDP-17 is found, it will be possible to determine whether a patient believed to have the sporadic form of frontotemporal dementia or dementia with tangles only carries the mutation and whether, patients with clinical and neuropathological features similar to FTDP-17, belonging to families in which not enough patients are available to perform linkage studies at this time, can be included in the group (8, 12, 18, 39, 40, 49, 50, 55, 58, 59).

Differences in the morphological and molecular characteristics of tau deposits in Seattle family A and MSTD suggest the possibilities that different mutations in the same gene or mutations in different genes cause the disease. It must be kept in mind that mutations in the Amyloid Precursor Protein gene can produce different phenotypes (68) and that in Machado-Joseph disease the same mutation can produce different phenotypes (32). Finding the gene causing FTDP-17 is of great importance, not only for understanding this disease, but also, if this gene is not the tau gene, a possibility which at this time has not been completely ruled out, its identification will give fundamental information on the mechanisms inducing tau aggregation and filament formation, not only in FTDP-17, but also in many other neurodegenerative diseases with tau deposits, whether accompanied or not by other neuropathological lesions such as amyloid deposits. Understanding the mechanisms that induce aggregation of tau into filaments will provide an important tool for the development of therapeutic strategies relevant to many different neurodegenerative diseases affecting individuals in middle and old age.

Acknowledgments

The authors wish to thank Drs R.A. Crowther, M. Farlow, M. Goedert, R. Jakes, J. Murrell, D.Nochlin, P.Poorkaj, G.Schellenberg and S.M.Sumi for useful discussions; C. Alyea, B. Dupree, F. Epperson, R. Funkhouser, and the Visual Aids Department of the MRC Laboratory of Molecular Biology for technical assistance. The work described was supported in part by the VA Research Funds, Metropolitan Life Foundation to T.D.B.and Public Health Service Grants AG05136 to T.D.B., NS29822 and AG10133 to B.G. and The Royal Society (London) Research Grant 23679 to M.G.S..

References

1. Andreadis A, Brown WM, Kosik KS (1992) Structure and novel exons of the human tau gene. *Biochem* 31: 10626-33
2. Arriagada PV, Growdon JH, Hedley-White ET, Hyman BT (1992) Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology* 42: 631-639
3. Baker M, Kwok JBJ, Kucera S, Crook R, Farrer M, Houlden H, Isaacs A, Lincoln S, Onstead L, Hardy J, Wittemberg L, Dodd P, Webb S, Hayward N, Tannenberg T, Andreadis T, Hallupp M, Schofield P, Dark F, Hutton M (1997) Localization of frontotemporal dementia with parkinsonism in an australian kindred to chromosome 17q21-22. *Ann Neurol* 42: 794-798
4. Bancher C, Jellinger KA (1994) Neurofibrillary tangle predominant form of senile dementia of Alzheimer's type: a rare subtype in very old subjects. *Acta Neuropathol* 88: 565-570
5. Basun H, Almkvist O, Axelman K, Brun A, Campbell TA, Collinge J, Forsell C, Froelich S, Wahlund L-O, Wetterberg L, Lannfelt L (1997) Clinical characteristics of a chromosome 17-linked rapidly progressive familial frontotemporal dementia. *Arch Neurol* 54: 539-544
6. Bird TD, Wijsman EM, Nochlin D, Leehey M, Sumi SM, Payami H, Poorkaj P, Nemens E, Rafkind M, Schellemberg GD (1997) Chromosome 17 and hereditary dementia: linkage studies in three non-Alzheimer families and kindreds with late-onset FAD. *Neurology* 48: 949-954
7. Braak H, Braak E (1991) Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol* 82: 239-259
8. Brown J, Lantos P, Stratton M, Roques P, Rossor M (1993) Familial progressive supranuclear palsy. *J Neurol Neurosurg Psychiatry* 56: 473-476
9. Brown J, Ashworth A, Gydesen S, Sorensen A, Rossor M, Hardy , Collinge J (1995) Familial non-specific dementia maps to chromosome 3. *Hum Mol Genet* 4: 1625-1628
10. Brun A, Englund B Gustafson L, Passant U Mann DMA Neary D, Snowden JS, The Lund and Manchester groups (1994) Consensus statement Clinical and neuropathological criteria for frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 57: 416-418
11. Chin S S-M, Goldman JG (1996) Glial inclusions in CNS degenerative diseases. *J Neuropathol Exp Neurol* 55: 499-508
12. Cole M, Write D, Banker BQ (1979) Familial aphasia: the Pick-Alzheimer spectrum. *Trans Am Neurol Ass* 104: 175-179
13. Conrad C, Andreadis A, Trojanowski JQ, Dickson DW, Kang D, Chen X, Wiederholt W, Hansen L, Masliah E, Thal L J, Katzman R, Xia Y, Saitoh T (1997) Genetic evidence for the involvement of τ in progressive supranuclear palsy. *Ann Neurol* 41: 277-281
14. Cordes M, Wszolek ZK, Calne DB, Rodnitzky RL, Pfeiffer RF (1992) Magnetic resonance imaging studies in rapidly progressive autosomal dominant parkinsonism and dementia with pallido-ponto-nigral degeneration. *Neurodegeneration* 1: 217-224
15. Couch FJ, Castilla LH, Xu J, Abel KJ, Welcsh P, King SE, Wong L, Ho PP, Merajver S, Brody LC, Yin G, Hayes ST, Gieser LM, Flejter WL, Glover TW, Friedman LR, Lynch ED, Meza J,E, King M-C, Law DJ, Deaven L, Bowcock AM, Collins FS, Weber BL, Chandrasekharappa SC (1995) A YAC-, P1-, and cosmid based physical map of the BRCA1 region on chromosome 17q21. *Genomics* 25: 264-273
16. Crowther RA (1991) Straight and paired helical filaments in Alzheimer disease have a common structural unit. *Proc Natl Acad Sci USA* 88: 2288-2292
17. Dark F (1997) A family with autosomal dominant non-Alzheimer's presenile dementia. *Australian and New Zealand J. Psychiatr* 31: 139-144
18. de Yébenes JG, Sarasa JL, Daniels SE, Lees AJ (1995) Familial progressive supranuclear palsy Description of a pedigree and review of the literature. *Brain* 118: 1095-1103
19. Feany MB, Dickson DW (1996) Neurodegenerative disorders with extensive tau pathology: a comparative study and review. *Ann Neurol*, 40: 139-148
20. Flament S, Delacourte A, Verny M, Hauw, JJ, Javoy-Agid F (1991) Abnormal tau proteins in progressive supranuclear palsy. Similarities and differences with the neurofibrillary degeneration of the Alzheimer type. *Acta Neuropathol* 81: 591-596
21. Foster NL, Wilhelmsen K, Sima AAF, Jones MZ, D'Amato C, Gilman S, Spillantini MG, Lynch T, Mayeux RP, Gaskell Ph-C, Hulette C, Pericak-Vance M A, Welsh-Bohmer KA, Dickson DW, Heutink P, Kros J, van Swieten JC, Arwert F, Ghetti B, Murrell J, Lannfelt L, Hutton M, Phelps CH, Snyder DS, Oliver E, Ball MJ, Cummings JL, Miller BL, Katzman R, Reed L, Schelper RL, Lanska DJ, Brun A, Fink JK, Khul DE, Knopman DS, Wszolek Z, Miller CL, Bird TD, Lendon C, Elechi C (1997) Frontotemporal Dementia and Parkinsonism Linked to Chromosome 17: A Consensus Statement. *Ann Neurol* 41: 706-715
22. Friedman LS, Ostermeyer EA, Lynch ED, Welcsh P, Szabo CI, Meza JE, Anderson LA, Dowd P, Lee MK, Rowell SE, Ellison J, Boyd J, King M-C (1995) 22 genes from chromosome 17q21: cloning sequencing and characterization of mutations in brest cancer families and tumors. *Genomics* 25: 256-263

23. Froelich S, Basun H, Forsell C, Lilius L, Axelman K, Andreadis A, Lannfelt L (1997) Mapping of a disease locus for familial rapidly progressive frontotemporal dementia to chromosome 17q12-21. *Am J Med Genet* 74: 380-385.
24. Giannakopoulos P, Hof PR, Bouras C (1995) Dementia lacking distinctive histopathology: clinicopathological evaluation of 32 cases. *Acta Neuropathol* 89: 346-355
25. Goedert M, Spillantini MG, Jakes R, Rutherford D, Crowther RA (1989) Multiple isoforms of human microtubule-associated protein tau: sequence and localization in neurofibrillary tangles of Alzheimer's disease. *Neuron* 3: 519-526
26. Goedert M, Spillantini MG, Potier MC, Ulrich J, Crowther RA (1989) Cloning and sequencing of the cDNA encoding an isoform of microtubule-associated protein tau containing four tandem repeats: differential expression of tau protein mRNAs in human brain. *EMBO J* 8: 393-399
27. Goedert M, Jakes R (1990) Expression of separate isoforms of human tau: correlation with the tau pattern in brain and effects on tubulin polymerization. *EMBO J* 9: 4225-4230
28. Goedert M, Spillantini MG, Cairns NJ, Crowther RA (1992) Tau proteins of Alzheimer paired helical filaments: abnormal phosphorylation of all six brain isoforms. *Neuron* 8: 159-168
29. Goedert M, Jakes R, Spillantini MG, Hasegawa M, Smith MJ, Crowther RA (1996) Sulphated glycosaminoglycans induce assembly of microtubule-associated protein tau into Alzheimer-like filaments. *Nature* 383: 550-553
30. Greenberg SG, Davies P (1990) A preparation of Alzheimer paired helical filaments that display distinct tau proteins by polyacrylamide gel electrophoresis. *Proc Natl Acad Sci USA* 87: 5827-5831
31. Greenberg SG, Davies P, Schein JD, Binder LI (1992) Hydrofluoric acid-treated tau PHF proteins display the same biochemical properties as normal tau. *J Biol Chem* 267: 564-569
32. Greenstein PE, Moore D, Levy-Lahad E, Stephens K, Bird TD (1996) Nine families with the SCA3/Machado-Joseph disease type of inherited ataxia. *Neurology* 47: 1106-1107
33. Groen JJ, Endtz LJ (1982) Hereditary Pick's disease: second re-examination of the large family and discussion of other hereditary cases, with particular reference to electroencephalography, a computerized tomography. *Brain* 105: 443-449
34. Gustafson L (1993) Clinical picture of frontal lobe degeneration of non-Alzheimer type. *Dementia* 4: 143-148
35. Haass C (1997) Presenilins: genes for life and death. *Neuron* 18, 687-690
36. Heutink P, Stevens M, Rizzu P, Bakker E, Kros JM, Tibben A, Niermeijer MF, van Duijn CM, Oostra BA, van Swieten JC (1997) Hereditary frontotemporal dementia is linked to chromosome 17q21-22: a genetic and clinicopathological study of three Dutch families. *Ann Neurol* 41: 150-159
37. Jackson M, Lowe J (1996) The new neuropathology of degenerative frontotemporal dementias. *Acta Neuropathol* 91: 127-134
38. Kamb A, Futreal PA, Rosenthal J, Cochran C, Harshman KD, Liu Q, Phelps RS, Tautigian SV, Tran T, Hussey C, Bell R, Miki Y, Swensen J, Hobbs MR, Marks J, Bennett LM, Barrett JC, Wiseman RW, Shattuck-Eidens D (1994) Localization of the VHR phosphatase gene and its analysis as a candidate for BRCA1. *Genomics* 23: 163-167
39. Kim RC, Collins GH, Parisi JE, Wright AW, Chu YB (1981) Familial dementia of adult onset with pathological findings of "non-specific" nature. *Brain* 104: 61-78
40. Knopman DS, Mastri AR, Frey WH, Sung JH, Rustan T (1990) Dementia lacking distinctive histologic features: a common non-Alzheimer degenerative dementia. *Neurology* 40: 251-256
41. Ksiezak-Reding H, Morgan K, Mattiace LA, Davies P, Kiu W-K, Yen S-H, Weidenheim K, Dickson DW (1994) Ultrastructure and biochemical composition of paired helical filaments in corticobasal degeneration. *Am J Pathol* 145: 1-13
42. Lanska DJ, Currier RD, Cohen M, Gambetti P, Smith EE, Bebin J, Jackson JF (1994) Whitehouse PJ, Markesbery WR : Familial progressive subcortical gliosis. *Neurology* 44: 1633-1643
43. Lendon CL, Shears S, Busfield F, Talbot CJ, Renner J, Morris JC, Goate AM (1994) Molecular genetics of hereditary dysphasic dementia. *Neurobiol Aging* 15 (Suppl): S128
44. Lee VM-Y, Balin BJ, Otvos L, Trojanowski JQ (1991) A68 a major subunit of paired helical filaments and derivatized forms of normal tau. *Science* 251: 675-678
45. Lynch T, Sano M, Marder KS (1994) Clinical characteristics of a family with chromosome 17-linked Dishinibition-Dementia-Parkinsonism-Amyotrophy Complex (DDPAC). *Neurology* 44: 1878-1884
46. Mann DMA, South PW, Snowden JS, Neary D (1993) Dementia of frontal lobe type: neuropathology and immunohistochemistry. *J Neurol Neurosurg Psychiatr* 56: 605-614
47. Mazoyer S, Gayther SA, Nagai MA, Smith SA, Dunning A, van Rensburg EJ, Albertsen H, White R, Ponder BAJ (1995) A gene (DLG2) located at 17q12-21 encodes a new homologue of the Drosophila tumor suppressor dlg-A. *Genomics* 28: 25-31
48. Miller BL, Cummings JL, Villanueva MJ, Boone K, Mehringer CM, Lesser IM, Mena I (1991) Frontal lobe degeneration: clinical, neuropsychological, and SPECT characteristics. *Neurology* 41: 1374-1382
49. Molloy F, Lynch T, Farrell (1995) Fronto-temporal dementia with Pick-like bodies in an Irish-American family - neuropathological findings. *J Neuropathol Exp Neurol* 54: 444-445
50. Morris JC, Cole M, Banker BQ, Wright D (1984) Hereditary dysphasic dementia and the Pick-Alzheimer spectrum. *Ann Neurol* 16: 455-466
51. Mulot SFC, Hughes K, Woodgett JR, Anderton BH, Hanger DP (1994) PHF-tau from Alzheimer's brain comprises four species on SDS-PAGE which can be mimicked by in vitro phosphorylation of human brain tau by glycogen synthase kinase 3β. *FEBS Lett* 349: 359-364

52. Murrell J, Koller D, Foroud T, Goedert M, Spillantini MG, Edenberg H, Farlow M, Ghetti B (1997) Familial multiple system tauopathy with presenile dementia localized to chromosome 17. *Am J Hum Gen* 61: 1131-1138

53. Neve RL, Harris P, Kosik KS, Kurnit DM, Donlon TA (1986) Identification of cDNA clones for the human microtubule associated protein tau and chromosomal localization of the genes for tau and microtubule-associated protein 2. *Mol Brain Res* 1: 271-280

54. Nishimura T, Ikeda H, Akiyama H, Arai T, Kondo H, Okochi M, Furiya Y, Mori H, Oda T, Kato M, Iseki E (1997) Glial tau-positive structures lack the sequence encoded by exon 3 of the tau protein gene. *Neurosci Lett* 224: 169-172

55. Passant U, Gustafson L, Brun A, Spectrum of frontal lobe dementia in a Swedish family. *Dementia* 4: 160-162

56. Petersen RB, Tabaton M, Chen SG, Monari L, Richardson SL, Lynches T, Manetto V, Lanska DJ, Markesbery WR, Currier RD, Autilio-Gambetti L, Wilhelmsen KC, Gambetti P (1995) Familial progressive subcortical gliosis: presence of prions and linkage to chromosome 17. *Neurology* 45: 1062-1067

57. Prusiner SB (1997) Prion diseases and the BSE crisis. *Science* 278: 245-251

58. Reed LA, Grabowski TJ, Schmidt ML, Morris JC, Goate A, Solodkin A, Van Hoesen GW, Schelper RL, Talbot CJ, Wragg MA, Trojanowski JQ (1997) Autosomal dominant dementia with widespread neurofibrillary tangles. *Ann Neurol* 42: 564-572

59. Schaumburg HH, Suzuki K (1968) Non-specific familial presenile dementia. *J Neurol Neurosurg Psychiatry* 31: 479-486

60. Schenk V W D (1959) Re-examination of a family with Pick's disease. *Ann Hum Genet* 23: 325-333

61. Schmidt ML, Huang R, Martin JA, Henley J, Mawal-Dewan M, Hurtig HI, Lee VM-Y, Trojanowski J Q (1996) Neurofibrillary tangles in progressive supranuclear palsy contain the same tau epitopes identified in Alzheimer's disease PHFtau. *J Neuropathol Exp Neurol* 55: 534-539

62. Sima AAF, Defendini R, Keohane C, D'Amato C, Foster NL, Parchi P, Gambetti M, Lynch T, Wilhelmsen KC (1996) The neuropathology of chromosome 17-linked dementia. *Ann Neurol* 39: 734-743

63. Spillantini MG, Crowther AR, Goedert M (1996) Comparative study of the neurofibrillary pathology of Alzheimer's disease and familial presenile dementia with only tangles. *Acta Neuropathol* 92: 42-48

64. Spillantini MG, Goedert M, Crowther RA, Murrell J, Farlow, MJ, Ghetti B (1997) Familial multiple system tauopathy: a new neurodegenerative disease of the brain with tau neurofibrillary pathology. *Proc Natl Acad Sci USA* 94: 4113-4118

65. Spillantini MG, Goedert M, Crowther RA, Murrell JR, Farlow MJ, Ghetti B (1997) Characterization of tau pathology in familial multiple system tauopathy with presenile dementia In: Alzheimer's disease: biology, diagnosis and therapeutics, eds Iqbal K, Winblad B, Nishimura T, Takeda M & Wisniewsky H, John Wiley & Sons Ltd, 213-223

66. Spillantini MG, Roses AD, Yamaoka LH, Gaskell PC, Welsh-Bohmer KA, Pericak-Vance MA, Hulette CM (1997) Neuropathological features of frontotemporal dementia and parkinsonism linked to chromosome 17q21-22 (FTDP-17): Duke family 1684. *Brain Pathol* 7: 1149

67. Sumi SM, Bird TD, Nochlin D, Raskind MA (1992) Familial presenile dementia with psychosis associated with cortical neurofibrillary tangles and degeneration of the amygdala. *Neurology* 42: 120-127

68. Tanzi R, Kovacs D, Kim T-W, Moir R, Gevenette S, Wasco W (1996) The gene defects responsible for familial Alzheimer's disease. *Neurobiol Dis* 3: 159-168

69. Tracz E, Dickson DW, Hainfeld JF, Ksiezak-Reding H (1997) Paired helical filaments in corticobasal degeneration: the fine fibrillary structure with Nano Van. *Brain Res* 773: 33-44

70. Ulrich J, Spillantini MG, Goedert M, Dukas L, Stähelin HB (1992) Abundant neurofibrillary tangles without senile plaques in a subset of patients with senile dementia. *Neurodegeneration* 1: 257-264

71. Vermersch P, Bordet R, Ledoze F, Ruchoux MM, Chapon F, Thomas P, Destée A, Lechevallier B (1995) Demonstration of a specific profile of pathological tau proteins in frontotemporal dementia cases. *CR Acad Sci* 318: 439-445

72. Wijker M, Wszolek ZK, Wolters ECH, Rooimans MA, Pals G, Pfeiffer RF, Lynch T, Rodnitzky RL, Wilhelmsen KC, Arwert F (1996) Localization of the gene for rapidly progressive autosomal dominant parkinsonism and dementia with pallido-ponto-nigral degeneration to chromosome 17q21. *Hum Mol Genet* 5: 151-154

73. Wilhelmsen KC (1997) Frontotemporal dementia is on the MAP τ. *Ann Neurol* 41: 139-140

74. Wilhelmsen KC, Lynch T, Pavlov E, Higgins M, Nygaard TG (1994) Localization of disinhibition-dementia-parkinsonism-amyotrophy complex to 17q21-22. *Am J Hum Genet* 55: 1159-1165

75. Wszolek ZK, Pfeiffer RF, Bhatt MH, Schelper RL, Cordes M, Snow BJ, Rodnitzky RL, Wolter SEC, Arwert F, Calne DB (1992) Rapidly progressive autosomal dominant parkinsonism and dementia with pallido-ponto-nigral degeneration. *Ann Neurol* 32: 312-320

76. Wszolek ZK, Lynch T, Wilhelmsen KC (1997) Rapidly progressive autosomal dominant parkinsonism and dementia with pallido-ponto-nigral degeneration (PPND) and disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC) are clinically distinct conditions that are both linked to 17q21-22. *Parkinsonism & Related Disorders* 3: 67-76

77. Yamada T, McGeer EG, Schelper RL, Wszolek ZK, McGeer PL, Pfeiffer RF, Rodnitzky RL (1993) Histological and biochemical pathology in a family with autosomal dominant parkinsonism and dementia. *Neurol Psychiatr Brain Res* 2: 26-35

78. Yamaoka LH, Welsh-Bohmer KA, Hulette CM, Gaskell P C, Murray M, Rimmler JL, Helms BR, Guerra M, Roses AD, Schmechel DE, Pericak-Vance MA (1996) Linkage of frontotemporal dementia to chromosome 17: clinical and neuropathological characterization of phenotype. *Am J Hum Genet* 59: 1306-1312

79. Zheng Y, Jung MK, Oakley BR (1991) γ-tubulin is present in Drosophila melanogaster and Homo sapiens and is associated with the centrosome. *Cell* 65: 817-823