Review article

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Frontotemporal dementia and parkinsonism linked to chromosome 17

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Abstract

Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) is an autosomal dominant neurodegenerative disorder caused by mutations in the MAPT gene which encodes the microtubule-associated protein tau. This hereditary tauopathy is a rare clinical syndrome, affecting approximately two hundred kindreds and about six hundred individuals bearing thirty nine known MAPT mutations. The disorder is thought to be related to the altered proportion of tau protein isoforms or the ability of tau to bind to microtubules and to promote microtubule assembly and organization. The clinical presentation of FTDP-17 includes behavioral, cognitive and motor abnormalities. This disorder has both a variable course and phenotype.

Gross neuropathological examination reveals brain atrophy, especially of the frontal and temporal lobes, and selective atrophy of the basal ganglia and brainstem nuclei. The major microscopic features of FTDP-17 demonstrate the presence of neurofibrillary tangles, neuropil threads and glial inclusions composed of insoluble tau protein. Distribution and amount of tau deposits vary, depending on the type of MAPT mutation. The definitive diagnosis of FTDP-17 requires a set of clinical and pathological features combined with a molecular genetic analysis. Currently, there is no known effective treatment for FTDP-17.

Key words: *familial parkinsonism, frontotemporal dementia and parkinsonism linked to chromosome 17, genetics, pathology, tau mutations, tauopathies.*

Introduction

Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) is a recently described autosomal dominant inherited disorder caused by mutations in the *MAPT* gene. The *MAPT* gene encodes the microtubule-associated tau protein. FTDP-17 is a rare neurological condition. Since the 1996 International Consensus Conference held in Ann Arbor, Michigan, which defined FTDP-17 [17], approximately 200 families with 39 pathogenic mutations in the *MAPT* gene have been identified. Altogether, about 600 patients have been described, including those who died in the antecedent generations (personal assessment). Families with *MAPT* gene mutations were identified in North America, Europe, Asia and Australia [80]. There are no documented cases of FTDP-17 in Poland [36,85].

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The disorder is thought to be related to the altered proportion of tau protein isoforms or the ability of tau to bind to microtubules and to promote microtubule assembly and organization [22,57]. Tau gene mutations are found in 25% of the cases with familial frontotemporal dementia (FTD), but the prevalence of tau mutations in sporadic cases is only 4% [72].

The clinical picture of FTDP-17, consisting of behavioral and personality changes, cognitive impairment and motor symptoms, varies between families with different mutations as well as between members of the same family [17,57,59,81]. Tau genotype correlates with the type of initial clinical presentation; H1/H1 genotype being associated with parkinsonian phenotype and H1/H2 with the FTD phenotype [3]. The variability of clinical and pathological pictures within one family bearing the same *MAPT* mutation suggests the existence of other genetic or environmental factors in addition to the mutated *MAPT* [15,57].

Clinical presentation of FTDP-17 and genotype/phenotype correlations have previously been described in detail [3,59,80,81].

Recently familial FTD with ubiquitin-positive and tau-negative inclusions was linked to a chromosomal region at 17q21 (FTDU-17) [8,10]. In these cases, mutations in *MAPT* were not found despite a detailed genetic analysis [10,57]. The clinical symptoms of FTDU-17 are similar to FTDP-17 and include personality changes, memory disturbances, cognitive impairment and parkinsonism [8].

Prior to the Consensus Conference several families known as pallido-ponto-nigral degeneration (PPND), multiple system tauopathy with dementia (MSTD), hereditary dysphasic disinhibition dementia (HDDP), disinhibition-dementia-parkinsonism-amyotrophy complex (DDPC) and others were clinically and pathologically characterized [18,59]. However, their phenotype was somewhat different and they were considered to represent separate syndromes. In 1994, Wilhelmsen et al. found linkage to the locus on the long arm of chromosome 17 (17q21-22) in a DDPC family [79]. Additional genetic studies demonstrated linkage to the same locus in other families [4,78]. The Consensus Conference helped to group all of these kindreds into a single category of FTDP-17. In 1998, it was documented that MAPT gene mutations segregate with disease phenotype [9, 14, 28].

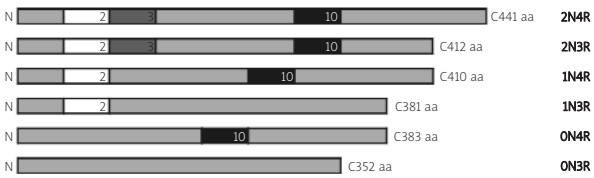

Fig. 1. Tau isoforms. Bars 2, 3 and 10 indicate alternatively spliced exons

Tau biology

Tau protein is necessary for stabilization and generation of microtubules, cell structures responsible mainly for axonal transport. In the human brain tau protein exists in 6 isoforms, generated by alternative splicing of exons 2, 3 and 10 [39]. Exons 2 and 3 code N-end 29-58 amino acid panels, responsible for three-dimensional orientation of microtubules [25,70]. Exon 10 codes for one of 4 (C-end) microtubule binding domains giving rise to 4R tau isoforms (Fig. 1). Isoforms 3R have a lower affinity to microtubules than

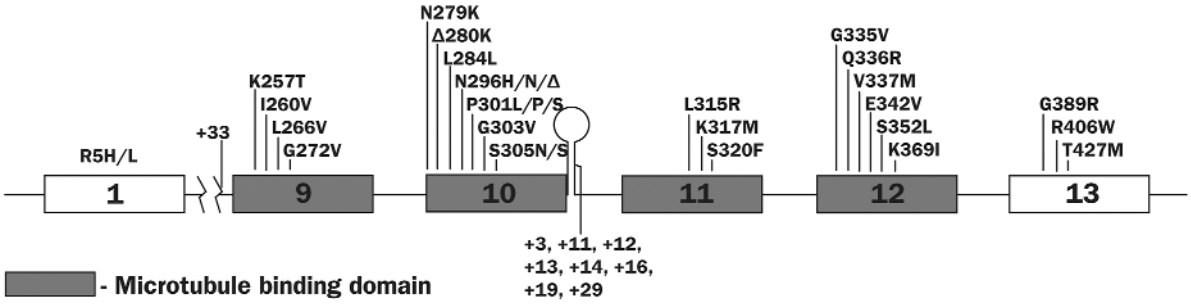

Fig. 2. Schematic representation of *MAPT* gene. The majority of *MAPT* mutations are localized in microtubule binding domains, or in their close proximity

Table I. *MAPT* gene mutations

Mutation	Localization, type	3R:4R ratio*	Given diagnosis	References
R5H	E1, missens	=	FTDP-17	[26]
R5L	E1, missens	=	PSP	[54,55]
K257T	E9 (R1), missens	=	PiD	[51,60]
I260V	E9 (R1), missens	=	FTD	[23]
L266V	E9 (R1), missens	=	PiD	[27,33]
G272V	E9 (R1), missens	=	PiD	[28]
E9+33	I9, splicing	N/A	FTD	[61]
N279K	E10 (IR 1/2), missens	>	PSP	[2,9,11,82]
D280K	E10 (IR 1/2), deletion	<	FTDP-17	[61]
L284L	E10 (IR 1/2), silent	>	FTD	[13]
N296H	E10 (R2), missens	>	FTDP-17	[30]
N296N	E10 (R2), silent	>	CBD	[71]
D296 N	E10 (R2), deletion	=	PSP	[50]
P301L	E10 (R2), missens	=	FTDP-17/PSP/CBD	[9,14,28,34,42,47,61]
P301P	E10 (R2), silent	=	PSP	[43]
P301S	E10 (R2), missens	=	FTDP-17 CBD	[7, 67]
G303V	E10 (R2), missens	>	PSP	[62]
S305N	E10 (IR 2/3), missens	>	CBD	[29]
S305S	E10 (IR 2/3), silent	>	PSP	[73]
E10+3	I10, splicing	>	FTDP-17	[69]
E10+11	I10, splicing	>	PSP	[37,43]
E10+12	I10, splicing	>	FTDP-17	[83]
E10+13	I10, splicing	>	FTDP-17	[28]
E10+14	I10, splicing	>	FTDP-17/ ALS	[28]
E10+16	I10, splicing	>	FTDP-17	[20,28,31,38,45,53]
E10+19	I10, splicing	<	FTD	[73]
E10+29	I10, splicing	<	FTD	[73]
L315R	E11, (IR 2/3), missens	=	PiD	[77]
K317M	E11, (IR 2/3), missens	=	PSP/CBD/ALS	[84]
S320F	E11, (R3), missens	=	PiD	[63]
G335V	E12, (IR3/4), missens	N/A	FTD	[1]
Q336R	E12, (IR 3/4), missens	=	FTD	[52]

Table I. continuation

V337M	E12, (IR 3/4), missens	=	FTDP-17	[54]
E342V	E12, (IR 3/4), missens	=	FTDP-17	[40]
S352L	E12, (R4), missens	=	Respiratory failure	[49]
K369I	E12, missens	=	PiD	[48]
G389R	E13, missens	=	PiD	[46,51]
R406W	E13, missens	=	PSP	[21]
T427M	E13, missens	N/A	FTD	[1]

*Abbreviations: ALS – amyotrophic lateral sclerosis; CBD – corticobasal degeneration; FTD – frontotemporal dementia; FTDP-17 – frontotemporal dementia with parkinsonism linked to chromosome 17, E – exon; I – intron; IR – region between R domains; N/A – data not available; PiD – Pick's disease; PSP – progressive supranuclear palsy; R – microtubule binding domain; * – as compared to normal conditions*

isoforms 4R. In physiological conditions all isoforms undergo phopshorylation by specific kinases. The phosphorylation level of tau protein regulates its interactions with microtubules. The same process probably regulates binding protein molecules to each other, which (in specific conditions) could lead to pathological accumulation of tau. The longest tau isoform has 79 serine and threonine potential phosphorous group acceptors. The acceptor group numbers decrease with length of the isoform. Most of these acceptor groups are located outside of microtubule binding domains [6]. The phosphorylation process is regulated by kinases, most of which are proline-dependent. These kinases include mitogen activated protein (MAP) kinases [12], glycogen synthase kinase 3B (GSK3B) [24], cyclin-dependent kinases 2 and 5, and stress-activated proteins' (SAP) kinases. In the regions without Ser and Thr groups phosphorylation is regulated by class II kinases, such as Ca^{2+}/calmodulin-dependent protein kinase II (CaMPKII), cyclic-AMP dependent kinase (CDK) and microtubule-affinity regulating kinases (MARK). In a normal brain the ratio of phosphorylation and dephosphorylation processes is equal. In pathological states this equilibrium is altered [6]. Isoforms 3R are also called 'fetal' MAP-tau, because they are predominant forms in the developing brain. Fetal forms of tau are more phosphorylated than 'adult' ones. Their binding to microtubules is weaker, allowing axons to grow during the maturation process. In an adult brain the ratio of 3R and 4R isoforms is close to 1 (with minimal dominance of 3R) [70]. *MAPT* mutations lead to the accumulation of protein and disturbances in microtubule functions. Accumulated tau is mostly insoluble and carries numbers of incorrect post-translational modifications. It also disturbs microtubule transport, leading to cell death through the deficiency of nutrients and structural molecules.

At the present time there are 39 known pathogenic mutations of *MAPT* gene, mainly localized around a microtubule binding domain area (Figure 2, Table I). The University of Antwerp database [1] also lists a silent L315L mutation. There are 18 non-pathogenic polymorphisms in *MAPT* gene listed on The University of Antwerp database [1] (not included in this review).

Neuropathology

Gross examination reveals brain atrophy with brain weight ranging from 720 to 1420 grams [2,43,58,77]. The degree of atrophy is variable and to some extent correlates with the stage of disease. In advanced stages atrophy may be conspicuous in the frontal and temporal lobes, caudate nucleus, putamen, globus pallidus, amygdala, hippocampus and hypothalamus (Fig. 3A) [17,27,30,48,59,72]. The anterior part of the frontal lobe is especially vulnerable to atrophy. The atrophy is frequently asymmetric, with a "knife-edge" appearance of the cerebral cortex in some cases [19,27,60,74]. The white matter of the temporal lobes and corpus callosum may be decreased in volume. In some cases atrophy of the midbrain and pons is observed (Fig. 3A). There is marked depigmentation of the substantia nigra and locus coeruleus (Fig. 3B) [23,26,30,58,60,62]. Mild atrophy of the cerebellar cortex and loss of pigment in the dentate nucleus may be seen [18,19,58,59,]. Gray and white matter

atrophy may be accompanied by enlargement of the lateral and third ventricles [19,26,27,30,74].

Microscopical findings in FTDP-17 include neuronal loss and astrocytic gliosis, present in varied distribution and severity in the cerebral cortex, underlying the white matter, basal ganglia and brainstem [16,69]. The neuronal loss in the cortex may be associated with microvacuolization and spongiosis in the superficial cortical layers [2,16,30,53,74]. Ballooned achromatic neurons can be seen in some cases (Fig.4A) [48,59,71,73]. Pick-like bodies, similar to those seen in Pick's disease (PiD) were found in some mutations (Fig 4B) [5,27,48,52,69] However, the neuropathologic hallmark of FTDP-17 is the presence of hyperphosphorylated tau protein deposits in neurons or in both neurons and glia of the cerebrum, cerebellum and brainstem [22,59,68]. Tau accumulation may also be seen in motor neurons of the spinal cord [2,15,30]. Neuronal tau pathology consists of neurofibillary degeneration with formation of classic flame- and globose-shaped neurofibrillary tangles (NFT) [17,64] or diffuse, granular deposits, called pretangles (Fig.5A,B) [7,26,84]. Thread-like structures (neuropil threads) and grains, seen in both grey and white matter, represent glial processes and axonal segments (Fig.5C) [11,35]. Astrocytic tau pathology demonstrates the presence of a granular tau staining pattern (Fig 5D), and structures reminiscent of the tufted astrocytes (as also observed in progressive supranuclear palsy, PSP) or astrocytic plaques (typical of corticobasal degeneration, CBD) [17,59,68]. Astrocytic plaques were described only in two

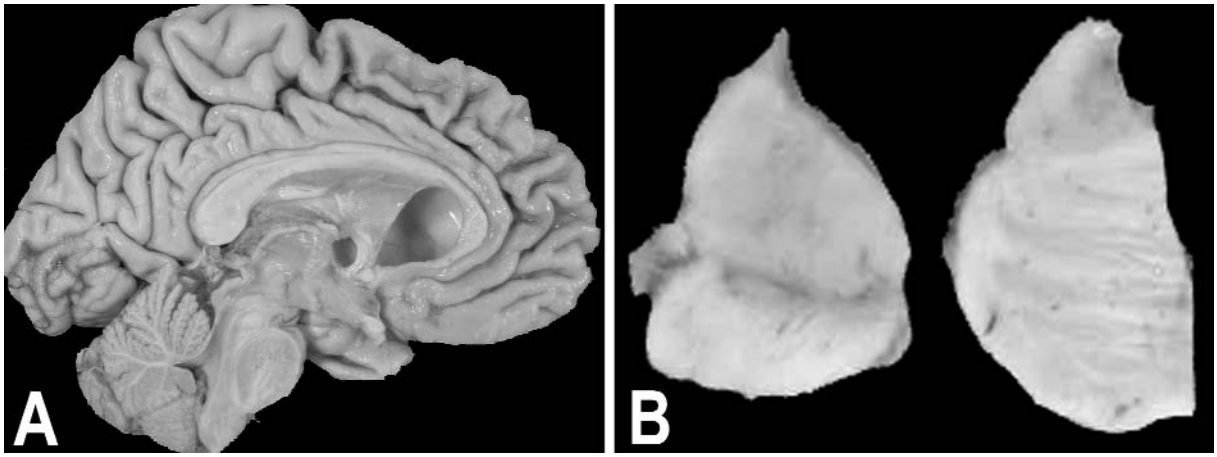

Fig. 3. A. The mid-sagittal section of fixed brain shows atrophy of the frontal cortex and brainstem. **B.** Depigmentation of the substantia nigra and locus coeruleus. S305N mutation

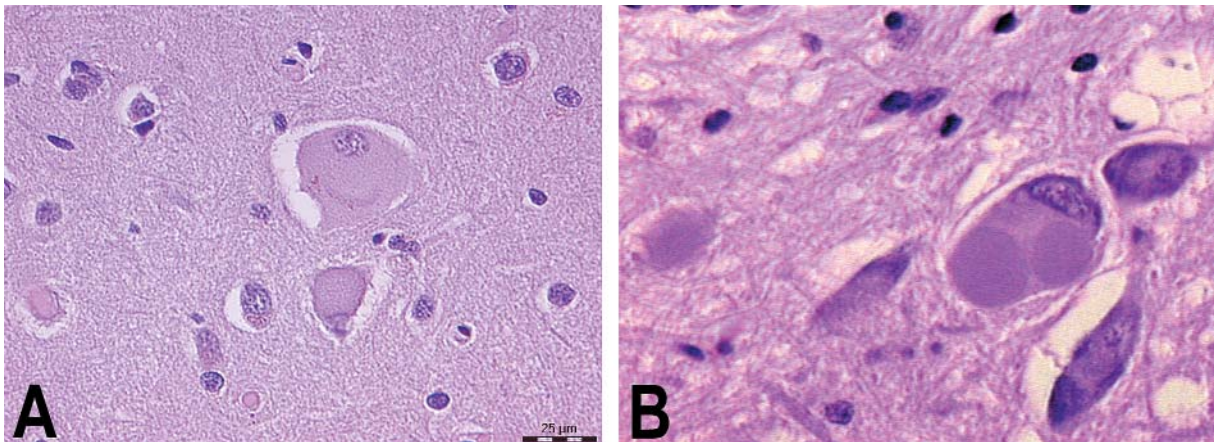

Fig. 4. A. Ballooned achromatic neuron in the cingulate gyrus. N279K mutation. **B.** Pick-like bodies within a neuron of the oculomotor nucleus. N279K mutation. H&E staining

mutations: K317M [84] and N279K [58]. The oligodendroglial tau deposits resemble coiled bodies described in other neurodegenartive diseases (Fig 5E) [29,59]. Both neuronal and glial tau inclusions can be identified with silver staining, including Bielschowsky, Bodian or Gallyas. However, they are most reliably identified with immunohistochemistry for tau protein, especially with antibodies specific for phosphorylation-dependent epitopes staining insoluble tau deposits [16]. The intensity and specific location of tau deposits within the CNS regions and different cell types vary depending on the type of *MAPT* mutation. Mutations in exons 9,11,12 and 13 are characterized by predominant neuronal tau deposits. Mutations in exons 1 and 10 and in the intron following exon 10 are characterized by both neuronal and glial tau deposition [18]. Generally, in cases with neuronal-only deposits, all six tau isoforms are detected, with predominance of 3R tau. In cases with mixed neuronal/glial tau pathology deposits consist predominantly of 4R tau isoform [57].

The detailed characteristic of neuropathological changes in FTDP-17 with regard to their topographical distribution in different mutations of *MAPT* is presented in table II.

Morphology of tau filaments in FTDP-17, seen in electron microscopy, is markedly heterogeneous and depends on the *MAPT* mutation type. Tau protein may have an appearance of straight filaments (e.g. in mutations R5L, P301S, E10+3,G389R), twisted filaments (S305S, E10+13, G389R), straight tubules (R5H, N296H, S305N), paired tubules (N279K), twisted ribbons

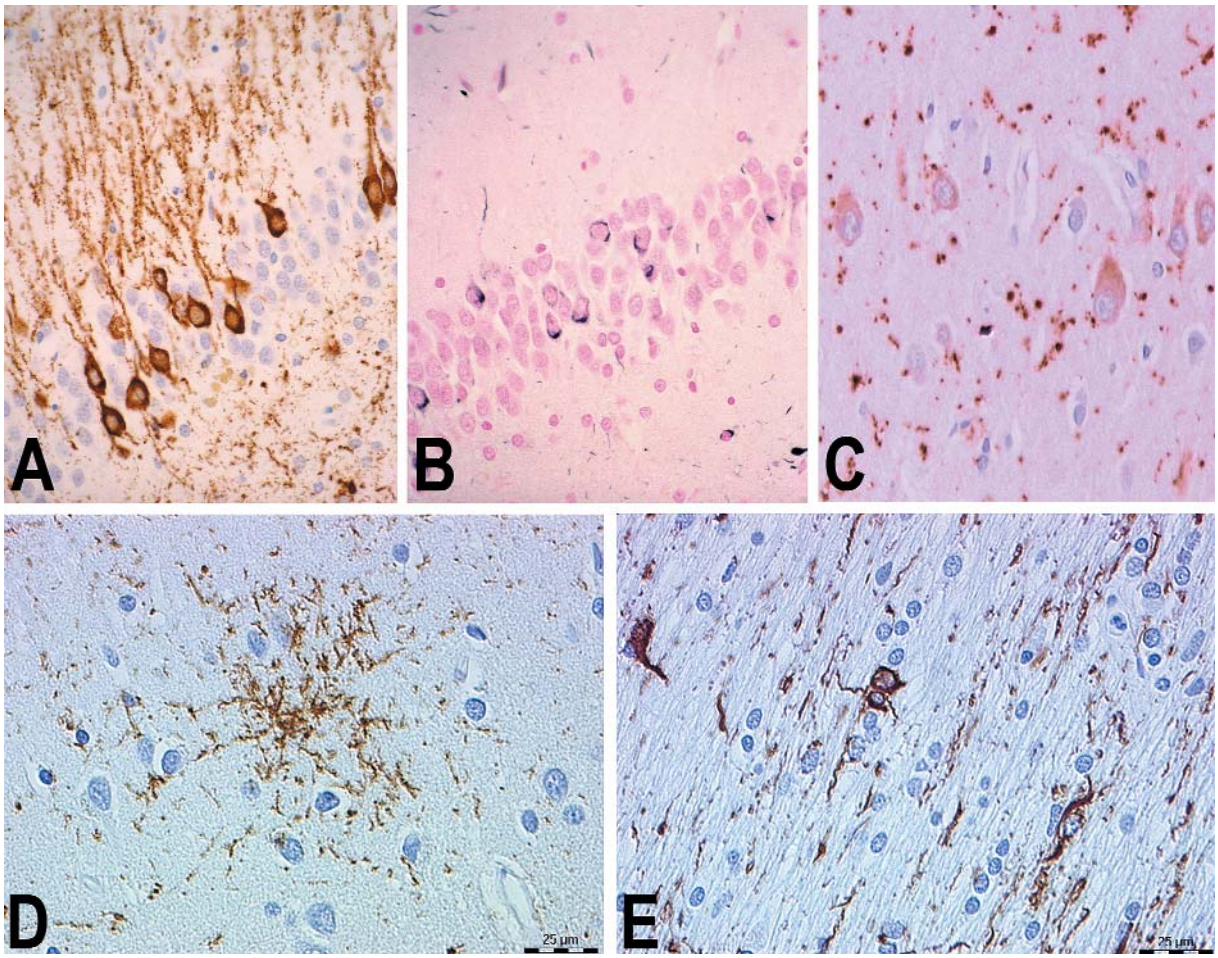

Fig. 5. A. Pretangles in neurons of the dentate fascia stain strongly with anti-tau antibodies. **B.** Pretangles are only partially stained with Gallyas impregnation. N279K mutation. **C.** Tau-positive grains in the amygdala. S305N mutation. **D.** Tau-postitive astrocyte in the frontal cortex. N279K mutation. **E.** Tau-positive coiled bodies in the corpus callosum. N279K mutation

Table II. Neuropathological features of FTDP-17 according to the mutated region of *MAPT* gene

Mutation	Histopathology				Tau pathology						Ref.
					Neuronal		Astrocytic		Oligoden-dro-glial	Neuronal/ glial	
	Neuronal loss	Gliosis	Ballooned neurons	Pretangles	Pick-like bodies	Not specified	Tufted astrocytes	Not specified	(coiled bodies)	(neuropil threads)	
Exon 1											
R5H	TL, MTL, PHipGy, Amy, SN	TL, MT, PHipGy, Amy, SN	N/A	motor Cx, PHipGy, RF	N/A	N/A	N/A	Cx	TL,FL	FL,TL	[26]
R5L	SN, LC, DN, Purk	DN, SN, LC	–	N/A	–	Put, GP, HyTh, Th, STN, SN, LC, BP	CaNu, Put, Th	N/A	PeriAq, BP	PeriAq, BP	[56]
Exon 9											
K257T	TL, Hip, Entorh, SN, LC	TL, Hip, Entorh	TL, Entorh	+	TL, Hip, Entorh, DG	+	N/A	+/-	N/A	+	[60, 69]
I260V	FL	FL	N/A	N/A	N/A	FL, Hip, DG	N/A	+	+	+	[23]
L266V	FL, TL, PL, Hip, Amy, CinGy, CaNu, SN	FL, TL, PL, Hip, CinGy, Amy, CaNu, Put	Amy	N/A	FL, TL, PL, CinGy, Hip, DG, CaNu, Put, SN	N/A	TL, SN	TL, BS	Cx & white matter	Cx & white matter	[27, 33]
G272V	FL, TL, MTL, PL, Ins, SN	FL, TL, PL, Ins	Entorh, BG	Hip	FL, TL, Hip, DG, CaNu, SN	FL, DG, Entorh, Amy, CaNu, Th	N/A	N/A	N/A	N/A	[5, 68]
Exon 10											
N279K	TL, CinGy, Amy, PHipGy, Hip, CaNu, Put, GP, Th, STN, SN, LC, DN	FTL, Entorh, Amy, CinGy, GP, STN, SN, LC, CB	FL, CinGy, Amy	+	+/–	Hip, DG, Amy, NMey, CaNu, Th, HyTh, GP, STN, PeriAq, SN, LC, ION, DN, SC	N/A	+/-	FL, TL, PL, CinGy, Hip, Entorh, GP, CaNu, Th, LC, HyTh, STN,	FTL, Amy, Th, HyTh, NMey, STN, GP, SN, PeriAq, LC, ION, DN, SC	[2, 11, 58]
L284L	N/A	N/A	N/A	Cx, Amy, Hip, PHipGy, BG, SN, RN	N/A	FTL, MT, PHipGy, Amy, BG, SN, RN	N/A	white matter	N/A	gray matter	[13]
N296H	FL, TL, Hip, Amy, NMey, CaNu, Th, SN, PeriAq, LC, raphe, RF	FL, TL, Hip, Amy, NMey, CaNu,Th, SN, PeriAq, LC, raphe, RF	Deep Cx layers	NeoCx, Hip, Entorh, Amy, HyTh, SN,LC, RF, SC	N/A	Amy, Th, STN, CaNu,Put, LC, RF, BS, SC	gray matter	N/A	Cx & white matter	gray & white matter	[15, 30]

Table II. continuation

N296N	N/A	N/A	+	+	N/A	FL, TL, Hip	N/A	FTL, Hip	N/A	N/A	[71]
ΔN296	BS	BS	N/A	N/A	N/A	Amy, Hip, Th, SN, LC	N/A	N/A	+	N/A	[15]
P301 L	FL, TL, Hip, Amy, CinGy, CaNu, Put, GP, Th, STN, SN, LC, ION, DN	FL, TL, gray/white matter junction, CaNu	+	FL, TL, PL, MT, DG, Entorh, PHipGy, BG, CinGy, SN	N/A	N/A	N/A	+	+	TL,PL, Hip,	[34, 44, 68]
P301S	loss of axons, sparing of U fibres	N/A	N/A	FL, TL, CaNu, SN	N/A	N/A	N/A	N/A	+	N/A	[7]
G303V	FL, TL, Hip, PHipGy, GP, STN, SN, LC, RN	FL, TL, SN, LC, RN	N/A	N/A	N/A	Hip, PHipGy, GP, STN, SN, LC, RN	N/A	PHipGy, Hip, GP, STN, SN, LC, RN	N/A	N/A	[62]
S305N	N/A	N/A	Ins	N/A	+	FL, TL,Ins, DG	N/A	N/A	Amy, Put, CaNu, GP, Th, STN, SN, RN, RF	Amy, S CaNu, GP, Put, Th, TN, SN, RN	[29, 32]
S305S	motor Cx, GP, STN, SN	motor Cx, STN,SN	FL, motor Cx,	N/A	–	Cx, PeriAq, Amy, SN	motor Cx,	N/A FL,TL, PL, Amy, Th	N/A	N/A	[73]
Intron following exon 10											
*+3,+11, +12,+13, +14,+16	NeoCx, Amy, CaNu, Put, GP, HyTh, SN, LC, BS, DN, SC	NeoCx, Amy, CaNu, Put, GP, HyTh	+	+	N/A	FL, TL, PL, NMey, HyTh, SN, LC, PeriAq, BS, DN	–	N/A	FL, TL	CaNu, Put, Th, Amy, pons	[16, 18, 37, 43, 53, 83]
+29	FL, TL, PL, Hip, Amy, CaNu	FL, TL	FL, TL, PL	–	–	–	–	–	–	–	[74]
Exon 11											
L315R	TL, Hip, DG, Amy, CaNu, Put, SN	FL, TL, PL, Th, SN	N/A	N/A	FL,TL, LC DG, Hip, CaNu, Put,	N/A	FL, TL, SN	N/A	N/A	N/A	[77]
K317M	FTL, SN, bulbar motor nuclei, ant. horn of SC	FTL, SN, bulbar motor nuclei	–	Hip	–	NeoCx, Hip, DG, Amy, CaNu, Put, Th, STN, BS	+	N/A	white matter	N/A	[84]

Table II. continuation

S320F	TL, Hip, Entorh, CinGy	TL, Hip, Entorh, CinGy	+	FL, TL, PL, Amy, DG	FL, TL, PL, Amy, DG	N/A	N/A	N/A	+/-	N/A	[18, 63]
Exon 12											
Q336R	FL, TL, Hip	FL, TL	N/A	NMeyn, Hip	+	FL, TL, Hip	N/A	+	N/A	+	[52]
V337M	NeoCx	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	TL, Hip, CinGy	[68]
E342V	FTL, PL, OL, Purk	FTL, PL, OL	N/A	N/A	Hip	Hip, DG	FL	N/A	N/A	gray & white matter	[40]
S352L	CB	Cx, Hip, Th, BS	N/A	N/A	N/A	Hip, DG, STN, BS	N/A	+	N/A	+	[49]
K369I	FL, TL, Hip, PHipGy, Amy, CaNu	FL, TL, PL	+	N/A	FL,TL, DG,PL, Ins, CinGy	N/A	IntCap, ExtCap	N/A	IntCap, ExtCap	N/A	[48]
Exon 13											
G389R	FL, TL, Ins, CinGy, CaNu, Put, GP, SN	FL, TL, CinGy, Ins, CaNu, Put, GP	N/A	+	FL, TL, DG, Amy, Ins, CinGy, pons	+/-	N/A	+	N/A	Cx, Put, GP, Th, ExtCap, IntCap	[19, 46]
R406W	MTL	N/A	limbic area	N/A	N/A basal forebrain	Ins, HyTh,	N/A	N/A	+	Ins, HyTh, basal forebrain	[64]

* As these mutations are characterized by similar neuropathological features and distribution of histopathological changes, they were grouped together. The severity of changes can vary from case to case.

+ = frequent; +/- = occasional; - = negative; N/A = data not available; Ref. = References

Abbreviations of anatomical terms:

Amy = amygdala; BG = basal ganglia; BP = basilar pons; BS = brainstem; CaNu = caudate nucleus; CB = cerebellum; CinGy = cingulate gyrus; Cx = cerebral cortex; DG = dentate gyrus; DN = dentate nucleus; Entorh = entorhinal cortex; ExtCap = external capsule; FL = frontal lobe; FTL = frontotemporal lobe; GP = globus pallidus; Hip = hippocampus; HyTh = hypothalamus; Ins = insula; IntCap = internal capsule; ION = inferior olivary nucleus; LC = locus coeruleus; MTL = medial temporal lobe; NeoCx = neocortex; NMey - nucleus basalis of Meynert; OL = occipital lobe; PeriAq = periaqueductal grey matter; PHipGy = parahippocampal gyrus; PL = parietal lobe; Purk = Purkinje cells; Put = putamen; RF = reticular formation; RN = red nucleus; SC = spinal cord; SN = substantia nigra; STN = subthalamic nucleus; Th = thalamus; TL = temporal lobe

(K257T, P301L, K369I) or paired helical filaments (V337M, G342V, R406W) (Fig. 6) [16,48,59,68]. Two different types of tau filaments may coexist in one particular MAPT mutation, e.g. straight and twisted filaments in G389R or S320F mutation [19,63].

Differential diagnosis

Clinically, FTDP-17 may mimic several other neurodegenerative diseases. In the absence of a positive family history and molecular genetic data FTDP-17 can be mistaken for dementive disorders such as PiD, FTD, argyrophilic grain disease and Alzheimer disease (AD), and movement disorders such as PSP, CBD or Parkinson's disease [22,41,57,58,59,72,75,80].

The neuronal tau pathology seen in FTDP-17 (NFT and Pick-like bodies) requires differential diagnosis with that of AD or PiD. The glial tau pathology (astrocytic plaques, tufted astrocytes, coiled bodies) resembles that of PSP and CBD [66]. The presence of family history and genetic analysis of tau mutation are of great value in the differential diagnosis of these diseases.

Neuroimaging studies (CT, MRI) can assist in the clinical differential diagnosis of FTDP-17 mainly by excluding other diseases, such as brain tumor, vascular disease or hydrocephalus [80].

Conclusions

The clinical, molecular genetic and pathological characterizations of FTDP-17 led to a much better understanding of basic cellular process dysfunctions occurring in other neurodegenerative disorders, including AD, PiD, PSP and CBD. It is hoped that further work on a FTDP-17 mouse model [65] will lead to the development of specific and perhaps even curative therapies for this condition that can be extrapolated to other dementive and extrapyramidal disorders.

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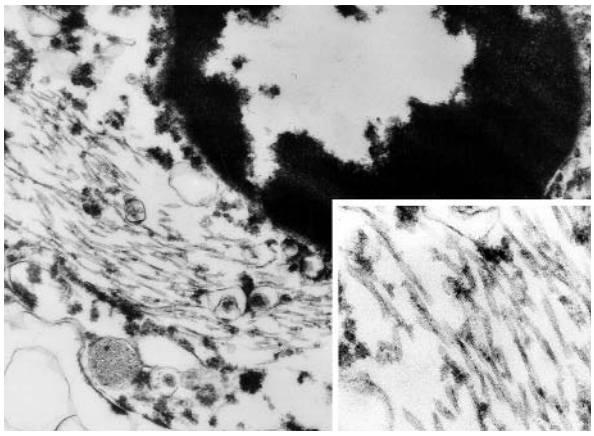

Fig. 6. Electron micrograph of an oligodendrocyte containing a coiled body. Twisted ribbon pattern of filaments is seen (inlet). S305N mutation. Courtesy of Dr W. Lin, Department of Neurosciences, Mayo Clinic, Jacksonville

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