Case report

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Frontotemporal lobar degeneration with *MAPT* mutation in an Italian-Polish family. A case report

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Abstract

Frontotemporal lobar degeneration (FTLD) with mutations in the MAPT (microtubule-associated protein tau) gene (FTLD with MAPT mutation) is a neurodegenerative disease with various clinical phenotypes. We present an Italian-Polish family with a IVS10+3G>A mutation in the MAPT gene, linked with haplotype H1s in a male proband (Fig. 2, II.2, H1s/H1b diplotype) and his sister (Fig. 2, II.1, the H1s/H1j diplotype). This report presents clinical, neuropathological and genetic testing of the proband and his affected sister, two members of an Italian-Polish family consisting of 25 family members. Their clinical history includes dementia as well as movement and cardiovascular disorders. Magnetic resonance imaging showed frontal and temporal cerebral atrophy. Neuropathological studies of the brain samples showed loss of neurons, gliosis, and the occurrence of neurofibrillary tangles, numerous neuropil threads, coiled bodies and abundant deposits of tau protein, including 3- and 4-repeated isoforms in neurons and glial cells. Only in the male proband brain, there were Pick body-like deposits in granule neurons of the hippocampus. Pathology of vascular walls was found in both cases. Ultrastructurally, the male proband showed clusters of collagen fibers mainly in a pericyte position. Beside the typical neurofibrillary pathology, aggregated gliofilaments and lipofuscin deposits in astroglia are described. Our report suggests that FTLD with IVS10+3G>A MAPT mutation causes damage mainly to the central nervous system and induces neuropathological changes, depending on the haplotypes of MAPT. In the clinical course of this disease, damage of the cardiovascular system may also be observed.

Key words: *FTLD, MAPT, H1 haplotypes, diplotypes H1s/H1j and H1s/H1b, tau isoforms.*

Introduction

Frontotemporal lobar degeneration (FTLD) represents a large heterogeneous group of familial and sporadic diseases, in which the neurodegenerative process involves mainly the frontal and temporal lobes (Fig. 1) [3]. The group of these diseases constitutes about 20% of presenile dementia cases [18]. Hereditary forms of FTLD are associated with mutations of multiple genes, including *MAPT* (microtubule-associated protein tau gene), *PGRN* (progranulin gene), *VCP* (valosin-containing protein gene), *$CHMP_2B$* (charged multivesicular body protein $_2$B gene),

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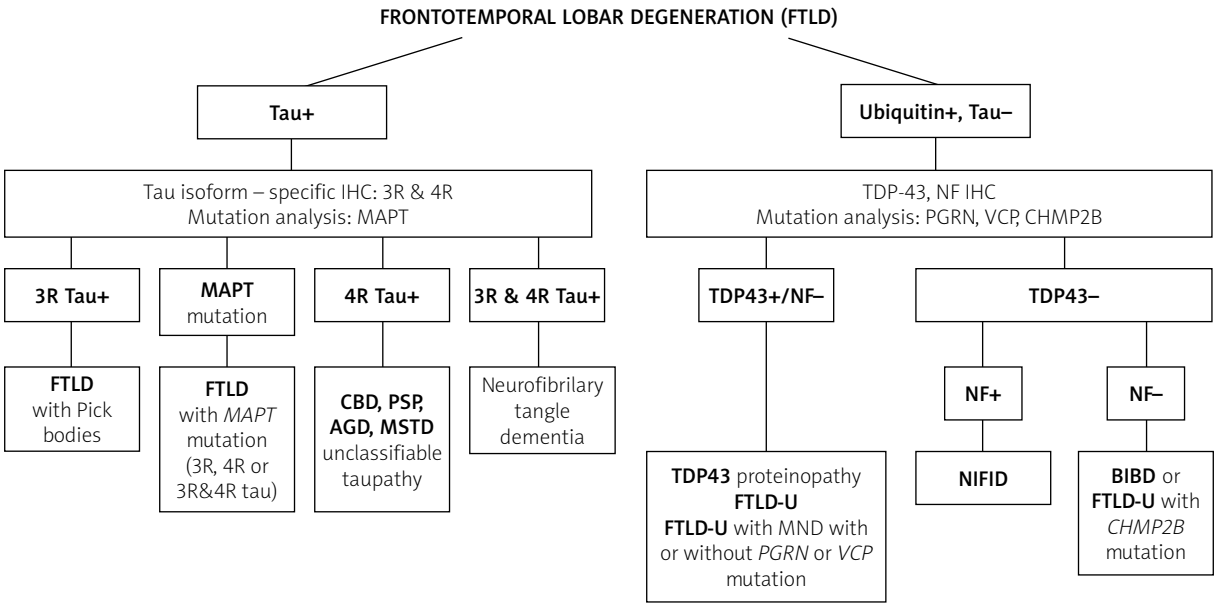

Fig. 1. Neuropathology algorithm flow chart for the diagnosis of frontotemporal lobar degeneration (FTLD) by Cairns *et al*. (Acta Neuropathol 2007; 114: 5-22). AGD – argyrophilic grain disease, BIBD – basophilic inclusion body disease, CBD – corticobasal degeneration, CHMP2B – charged multivesicular body protein 2B gene, FTLD-U – FTLD with ubiquitin-positive, tau-negative inclusions, IHC – immunohistochemistry, MAPT – microtubule-associated protein tau gene, MSTD – sporadic multiple system tauopathy with dementia, NIFID – neuronal intermediate filament inclusion disease, NF – neurofilament, PGRN – progranulin gene, PSP – progressive supranuclear palsy, TDP-43 – TAR DNA-binding protein 43, Tau – tau protein, VCP – valosin-containing protein gene.

TDP-43 (TAR DNA-binding protein 43) and other mutations [4,17]. *MAPT* mutations are identified in up to 20% of familial FTLD [9,20]. The *MAPT* gene codes the microtubule-associated protein tau, which is involved in microtubule assembly and stabilization, neuronal polarity, and axonal transport in the brain [7,20]. The tau protein is mainly synthesized in the peripheral and central nervous system (central nervous system [CNS], neurons and neuroglia), but it is also expressed in other tissues (heart, skeletal muscle, lung, kidney and others) [1,8,16]. The *MAPT* gene locus on chromosome 17 q21 has two major haplotypes, H1 and H2. *MAPT* consists of 16 exons and encodes 6 human brain isoforms of tau protein with 3 or 4 repeat domains (3R and 4R) [2,5,15]. Tau protein inclusions in different tauopathies have specific morphology and distribution. In the nervous system of FTLD patients carrying the *MAPT* mutation, inclusions of both 3R tau and 4R isoforms of tau protein are found. The 3R isoform of tau protein inclusions are observed in FTLD with Pick bodies, while the 4R isoform of tau protein occurs, inter alia, in such diseases as corticobasal degeneration, progressive supranuclear palsy and argyrophilic grain disease [6]. More than 40 mutations have been identified in the *MAPT* gene in individuals from more than 100 families with FTLD [6,12,27]. Depending on the mutation in the *MAPT* gene, we can observe different neuropathologic and clinical symptoms. There are also differences between family members and families suffering from FTLD with the same *MAPT* mutations. The main hallmarks of this disease are neurofibrillary pathology, neuronal inclusions, tau-positive neuroglial inclusions, both in astrocytic and oligodendrocytic cells and also the coiled bodies [5,11,13,26]. In this study, we investigated immunohistochemically, using antibodies against 3R- and 4R-tau isoforms, genetic and ultrastructural features of two members of Italian-Polish familial FTLD with dementia and movement disorders.

Material and methods

The reported cases

The pedigree consists of 25 Italian-Polish family members in four generations. The first tested pro-

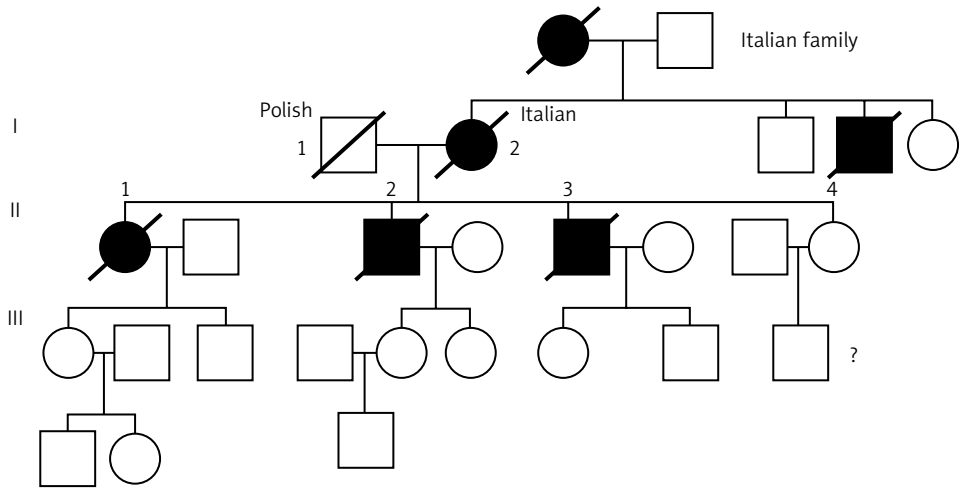

Fig. 2. Pedigree of the frontotemporal lobar degeneration with *MAPT* mutation of the Italian- Polish family. I.2 Italian grandmother, her mother and brother also with dementia and movement disorders in the family medical history. **I.1** grandfather (Pole) without symptoms. **II.2** the first tested male proband with mutation in *MAPT* gene, **II.1** his sister with mutation in *MAPT* gene, **II.3** brother with dementia and movement disorders in the family medical history, **III.** family members were not examined, currently without clinical symptoms.

band, a 58-year-old man (Fig. 2, II.2), died one year after the onset of the first dementia symptoms. At the age of 49, he had a cardiac pacemaker implanted. The patient complained of muscle weakness. At the end of his life, bulbar syndrome occurred. The diagnosis of Alzheimer's disease was suspected. The proband's sister (Fig. 2, II.1) died at the age of 68. She presented with behavioral abnormalities from the age of 59. Primarily, the loss of awareness, memory, interest and empathy was noted. Gradually social withdrawal and logopenic aphasia progressed. At the age of 61 she was afflicted by brain hemorrhagic stroke. At the end of her life, pyramidal and Parkinsonian syndromes were reported. Magnetic resonance imaging (MRI) showed cerebral atrophy in frontal and temporal lobes (Fig. 3).

Methods

Brain examinations were performed. Samples were taken from the brain structures of the affected male proband (II.2) and his sister (II.1). They were fixed in 10% buffered formalin and paraffin embedded. The specimens were stained with hematoxylin-eosin, Bielshowsky, Yamamoto, and Gallyas methods. Immunohistochemical studies were performed with antibodies to glial fibrillary acidic protein (GFAP, DAKO 1 : 70), anti-tau (DAKO 1 : 100), anti-Tau, 3R-re-

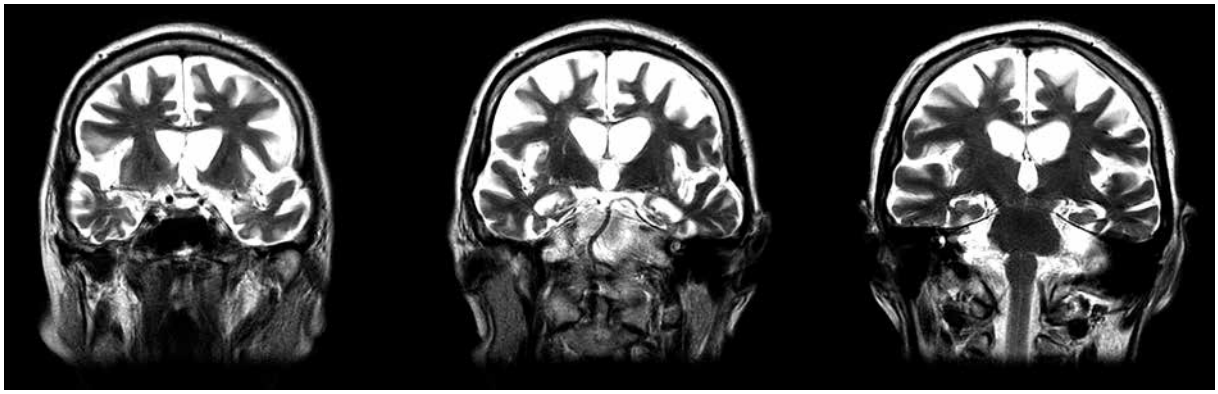

Fig. 3. Magnetic resonance imaging scans of frontotemporal lobar degeneration with *MAPT* mutation. Case II.1 sister (6 years of disease). Atrophy of frontal and temporal lobes.

peated isoform RD3 (Millipore, 1 : 1000), anti-tau-4R repeated isoform RD4 (Millipore, 1 : 1000), ubiquitin (DAKO, 1 : 35), β-amyloid (DAKO, 1 : 70) and α-synuclein (Leica, 1 : 20). For electron microscope evaluation small fragments of brains were taken from formalin or paraffin blocks. After deparaffinizing and/or washing in water, the material was fixed in 2.5% glutaraldehyde and postfixed in 2% OsO4, then routinely processed to Spurr resin. Ultrathin sections were stained with uranyl acetate and lead citrate and examined in an electron microscope (Opton DPS 109). Blood samples for DNA analysis were protected. Genomic DNA was isolated from peripheral blood leukocytes using standard methods. The male proband was screened for mutations in: *PSEN1*, *APP*, *PGRN*, *MAPT*, and *C9ORF72*. The presence of the mutation also was confirmed in the proband's sister. The absence of the mutation IVS10+3G> A *MAPT* was confirmed in the control group of 150 elderly, neurologically healthy subjects from the Polish population. Haplotype associated with the mutation was identified by the presence or absence of 238 bp deletion in intron 9 and by genotyping five SNPs (rs1467967, rs242557, rs3785883, rs2471738 and rs7521) [22]. The mutation-associated haplotype was determined based on the comparison of diplotypes identified in the male proband and his sister.

Results

In both cases, the gross examination of the brains showed moderate symmetrical cortical atrophy in the frontal and temporal lobes. There was mild atrophy of the anterior part of the caudate nucleus, while other subcortical structures were normal. The lateral ventricles were intensively dilated. The substantia nigra of the mesencephalon and locus coeruleus of the pons were moderately depigmented. The cerebellum seemed to be normal. Routine histology of the light microscopy examination showed neocortical neuronal loss, mostly in the frontal and temporal lobes in layers II and III and also in the substantia nigra. This change was accompanied by moderate spongiosis and astrogliosis. Sections stained with either the Bielschowski, Yammamoto or Gallyas silver technique showed neurofibrillary tangles (NFTs) and neuropil threads (NTs) (Fig. 4A,B). Silver-stained fibrillary inclusions were found in Purkinje cells and neurons of the substantia nigra and also in the locus coeruleus (Fig. 4C-E). Numerous coiled bodies were observed in the white matter in frontal and temporal lobes (Fig. 4F,G). Ballooned neurons were detected in the pons and in the cerebral and cerebellar cortices (Fig. 4H). Tau-immunoreactive methods detected many more NFTs, coiled bodies and NTs than silver methods. Tau-immunoreactive deposits were abundant in the frontal and temporal cortex but also in the brainstem. They were visible in the form of granular deposits, tau-positive abundant neurites, neuropil threads, coiled bodies, Pick bodies, ballooned neurons and grain-like deposits (Fig. 5 and 6). Tau-3 repeated isoform positive Pick bodies in the granule neurons of the dentate gyrus of the hippocampus occurred only in the male proband (Fig. 5C), whereas intracytoplasmic deposits of tau-4 repeated isoform were observed in both cases (Fig. 5D and 6E). In the frontal cortex of the sister, tau-positive Pick bodies-like deposits were visible (Fig. 6F). A GFAP-positive tufted and monstrous astrocytes were observed mainly in the sister (Fig. 2, II.1) (Fig. 6H and 6J). Pathology of vascular walls was visible in both cases (Fig. 5J and 6J). Ultrastructural analysis of fibrillary inclusions showed tightly aggregated filaments of neurofibrillary tangles in the cytoplasm of nerve cells (Fig. 7). Astrocytes were often swollen with only a few short gliofilaments or with numerous gliofilaments filling the cytoplasm (Fig. 8). In their cytoplasm, lipofuscin deposits were located in the adjacent gliofilaments (Fig. 8). In capillaries, abundant collagen fibers were frequently found in the pericyte position and small clusters in different locations of the basement membrane (Fig. 9).

The analysis of the nucleotide sequence of the *MAPT* gene revealed an intron 10+3-splice site mutation (IVS10+3G>A, g.123806G>A) in both affected siblings. The analysis of diplotypes associated with mutation in the male proband and his sister showed that the IVS10+3G>A mutation was in the haplotype H1s background. The *MAPT* diplotype of the male proband was H1s/H1b, and that of his sister was H1s/H1j (Table I).

Discussion

We present a comprehensive analysis of members of the first Italian-Polish family with genetically confirmed FTLD with the IVS10+3G>A *MAPT* mutation. The mutation was previously reported as pathologic in another European population [19,26,28] and was absent in 138 patients with FTLD in the Polish population (data not published). The analysis of the *MAPT* gene in the two described cases showed

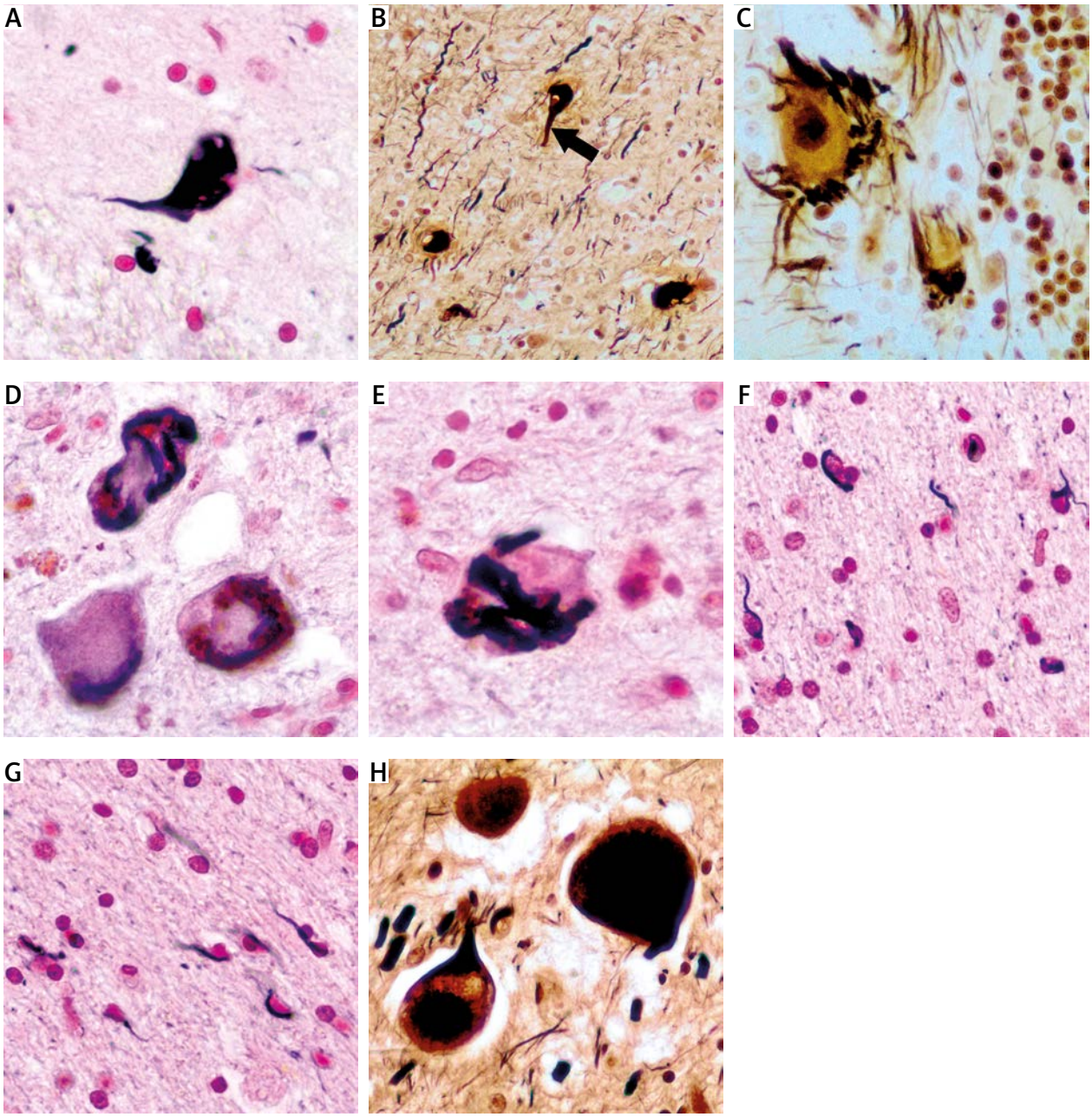

Fig. 4. Frontotemporal lobar degeneration (FTLD) with *MAPT* mutation. Silver techniques. **A)** Proband II.2. Pons. Neurofibrillary tangle (NFT). Gallyash. × 20. **B)** Case II.2. Temporal lobe, case II.2. Fibrillary material surrounds the nucleus and extends into the axon (arrow). Numerous neuropil threads. Yamamoto × 20. **C)** Case II.2. Purkinje cell. Nucleus surrounded by densely packed neurofibers. Yamammoto. × 40. **D)** Case II.1. Mesencephalon. Intracytoplasmic argyrophilic depots. Gallyas. × 40. **E)** Case II.1. Pons. Argyrophilic deposits. Gallyas. × 40. **F)** Case II.2. Coiled bodies in white matter of frontal lobe. Gallyas. × 40. **G)** Case II.1. Coiled bodies in white matter of temporal bodies. Gallyas. × 40. **H)** Case II.2. Ballooned neurons in the pons. Yamammoto. × 40.

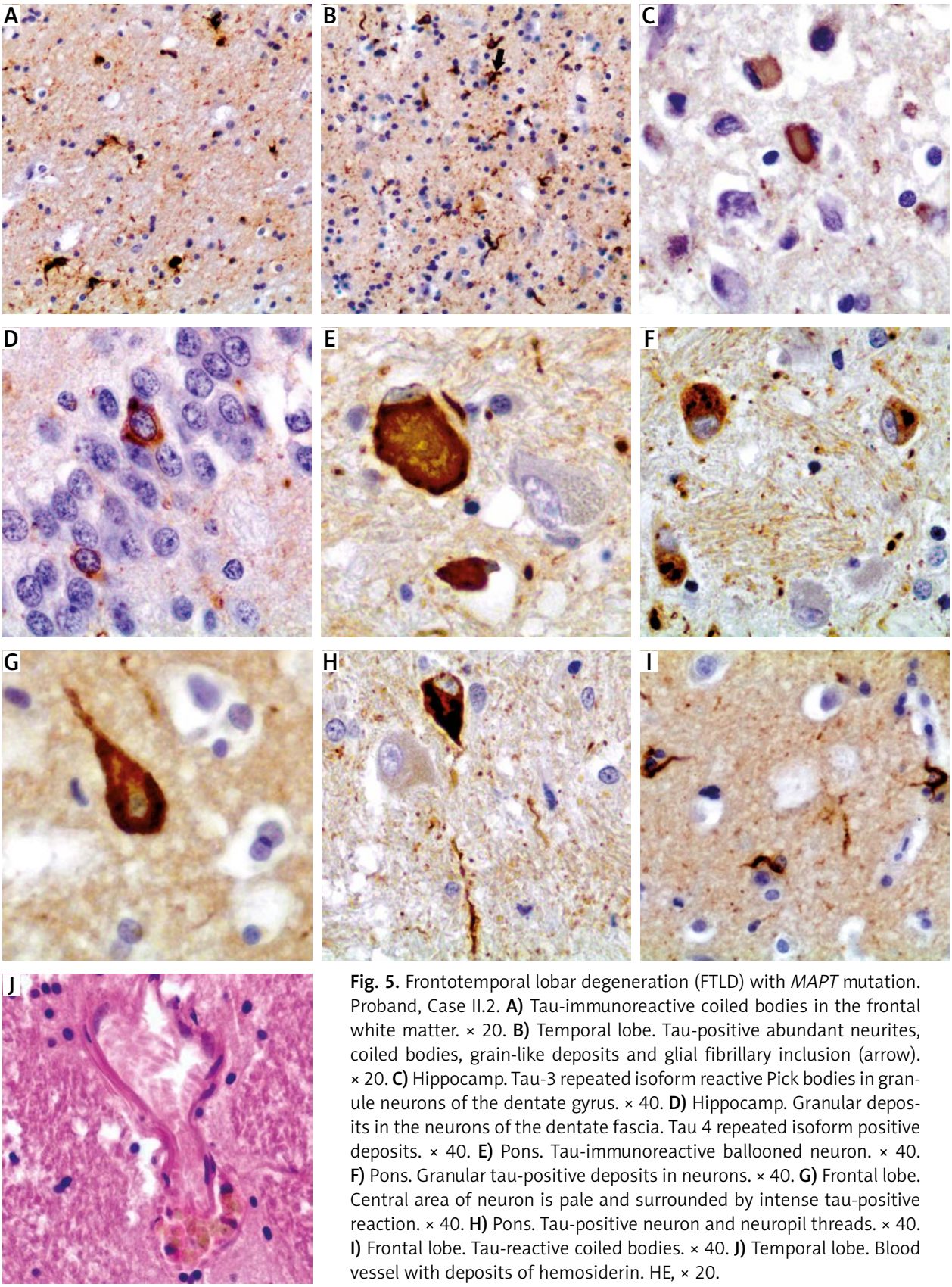

Fig. 5. Frontotemporal lobar degeneration (FTLD) with *MAPT* mutation. Proband, Case II.2. **A)** Tau-immunoreactive coiled bodies in the frontal white matter. × 20. **B)** Temporal lobe. Tau-positive abundant neurites, coiled bodies, grain-like deposits and glial fibrillary inclusion (arrow). × 20. **C)** Hippocamp. Tau-3 repeated isoform reactive Pick bodies in granule neurons of the dentate gyrus. × 40. **D)** Hippocamp. Granular deposits in the neurons of the dentate fascia. Tau 4 repeated isoform positive deposits. × 40. **E)** Pons. Tau-immunoreactive ballooned neuron. × 40. **F)** Pons. Granular tau-positive deposits in neurons. × 40. **G)** Frontal lobe. Central area of neuron is pale and surrounded by intense tau-positive reaction. × 40. **H)** Pons. Tau-positive neuron and neuropil threads. × 40. **I)** Frontal lobe. Tau-reactive coiled bodies. × 40. **J)** Temporal lobe. Blood vessel with deposits of hemosiderin. HE, × 20.

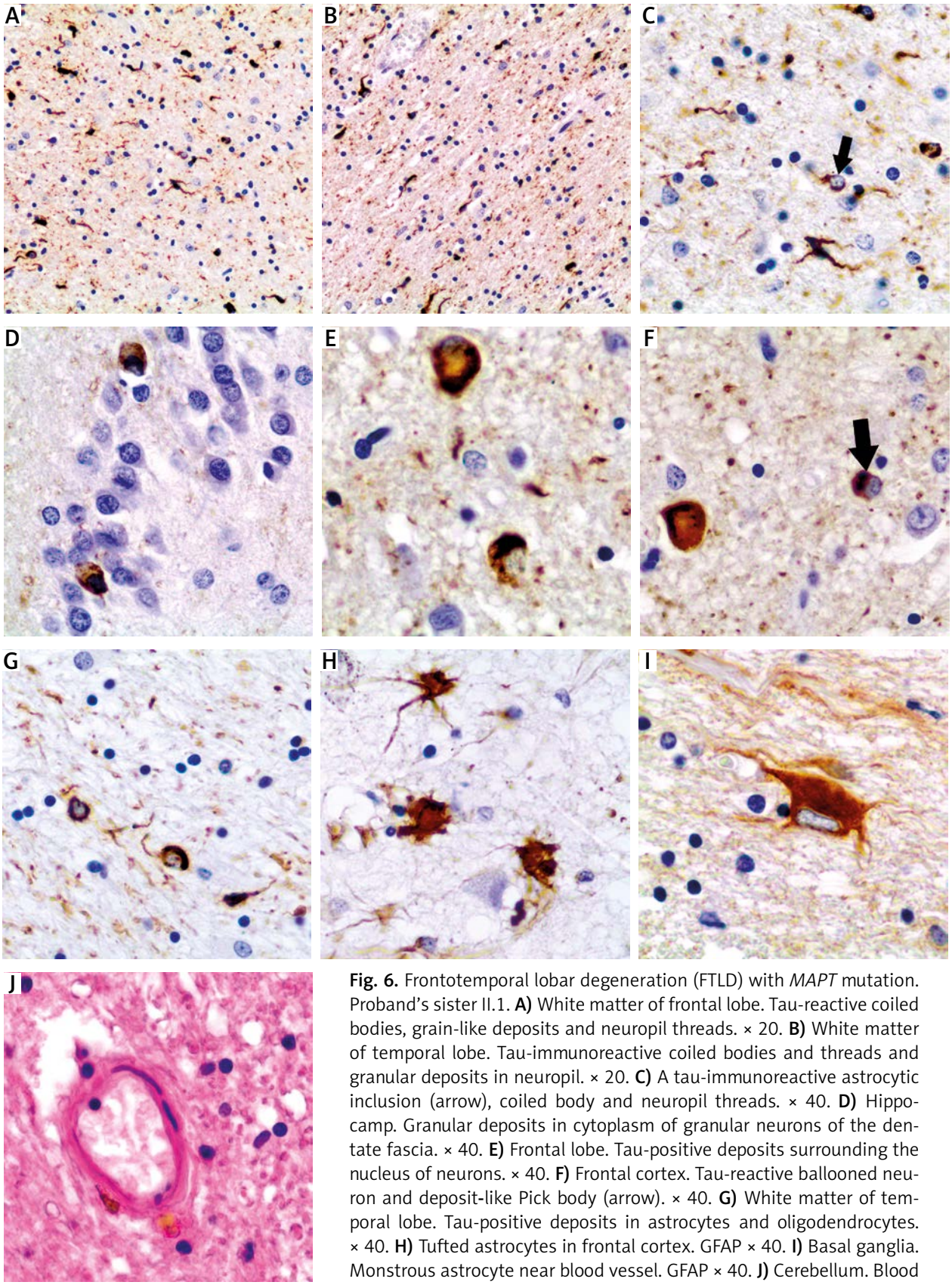

Fig. 6. Frontotemporal lobar degeneration (FTLD) with *MAPT* mutation. Proband's sister II.1. **A)** White matter of frontal lobe. Tau-reactive coiled bodies, grain-like deposits and neuropil threads. × 20. **B)** White matter of temporal lobe. Tau-immunoreactive coiled bodies and threads and granular deposits in neuropil. × 20. **C)** A tau-immunoreactive astrocytic inclusion (arrow), coiled body and neuropil threads. × 40. **D)** Hippocamp. Granular deposits in cytoplasm of granular neurons of the dentate fascia. × 40. **E)** Frontal lobe. Tau-positive deposits surrounding the nucleus of neurons. × 40. **F)** Frontal cortex. Tau-reactive ballooned neuron and deposit-like Pick body (arrow). × 40. **G)** White matter of temporal lobe. Tau-positive deposits in astrocytes and oligodendrocytes. × 40. **H)** Tufted astrocytes in frontal cortex. GFAP × 40. **I)** Basal ganglia. Monstrous astrocyte near blood vessel. GFAP × 40. **J)** Cerebellum. Blood vessel with deposits of hemosiderin. HE × 40.

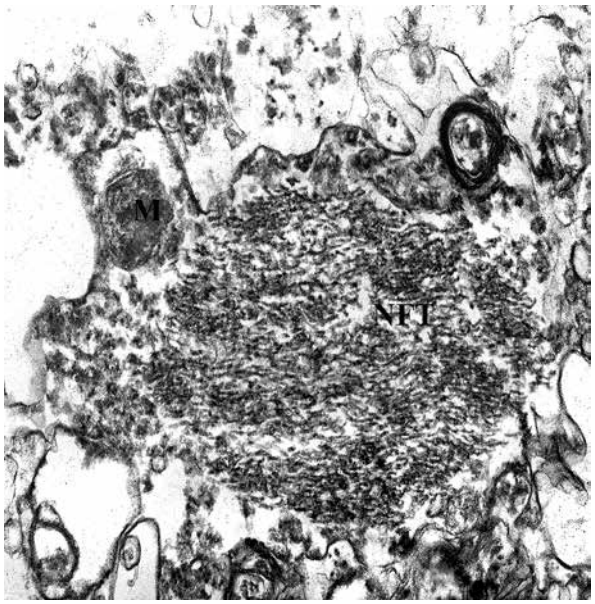

Fig. 7. Case II.1. Nerve cell cytoplasm with tightly aggregated filaments of neurofibrillary tangles (NFT). M – mitochondrium. Org. mag. × 12000.

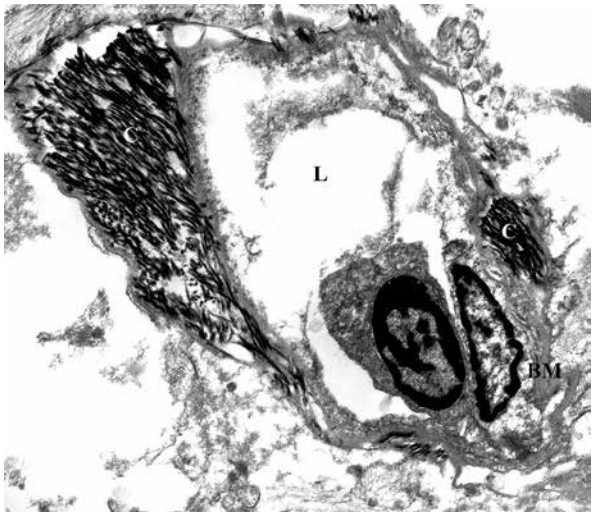

Fig. 9. Proband. Case II.2. Capillary. Collagen fibers (C) in the basement membrane (BM) and in the pericyte position. L – lumen. Orig. mag. × 4400.

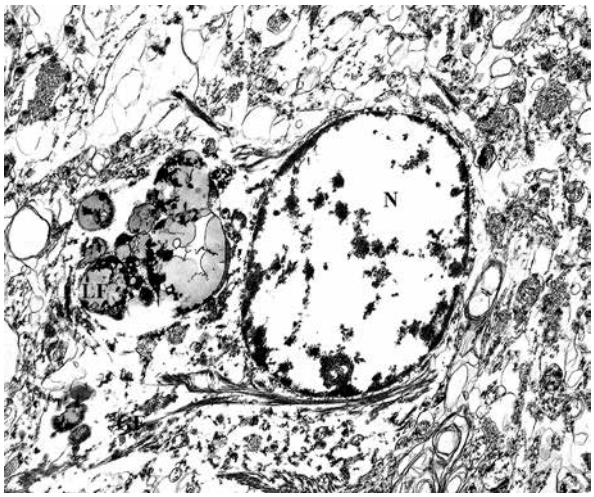

Fig. 8. Case II.1. Astrocyte with numerous bundles of gliofilaments (GF) and lipofuscin (LF) in the cytoplasm. N – nucleus. Orig. mag. × 4400.

that the IVS10+3G>A mutation was in the haplotype H1s background. There were differences in the *MAPT* diplotypes. The male proband's diplotype was H1s/H1b, while his sister's was H1s/H1j. It is possible that these variations affected the differences in the clinical course of the disease and in its neuropathological picture [28]. The male proband died one year after the onset of symptoms of dementia and 9 years after implantation of a cardiac pacemaker. The sister of the proband experienced brain hemorrhagic stroke 2 years after disease onset and died 9 years after the first symptoms of dementia. The mutation in the microtubule protein tau (*MAPT*) gene locus into haplotype H1 affected tau microtubule assembly and tau mRNA splicing. In addition, the increased inclusion of exon 10 in transcripts show an imbalance in the 3R and 4R tau isoforms [2,9,15].

The ratio of these two isoforms in normal conditions is generally equal (1 : 1), but it varies depending on the type of mutation [24]. Corticobasal degeneration (CBD) is characterized by increased 4R tau,

Table I. Mutation analysis of *MAPT* gene – ideogram

	Rs1467967	Rs242557	Rs3785883	Rs2471738	Del-in9	IVS10+3	Rs7521
Proband	G/G	G/G	G/G	C/C	H1/H1	G/A	G/A
Shared alleles	G	G	G	C	H1	A	G
Sister	A/G	G/G	G/G	C/C	H1/H1	G/A	G/G

whereas frontotemporal lobar degeneration with Pick bodies shares an overabundance of 3R tau (Fig. 1). FTLD with *MAPT* mutation is a biochemically heterogeneous disease associated with 3R and 4R tau deposits in various proportions, influencing the type of neuropathological changes. The main cellular function of tau protein is to assemble and stabilize microtubules and neural integrity. The aggregation of microtubules and creation of NFTs may be regarded as "toxic intensification" of their function in neurons [21,23]. These disorders may start aging processes leading finally to apoptosis. The clinical course of FTLD with *MAPT* mutation is also heterogeneous, because of the tau protein function in the cells outside the nervous system [1,8,16]. Ultrastructurally, in both cases, we observed neurofibrillary pathology and deposits of collagen in the vessel walls of the male proband's brain [10]. Šerý *et al*. [24] suggest that vascular pathology influences pathological processes in Alzheimer's disease [14]. Our report suggests that FTLD with *MAPT* mutation affects mainly the CNS, and neuropathological changes depend on the variant of the mutation. In the clinical course of this disease, damage of the cardiovascular system may also be observed.

Disclosure

Authors report no conflict of interest.

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