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Three sib-pairs of autopsy-confirmed progressive supranuclear palsy

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ABSTRACT

Objective: To describe the clinical, pathological, and genetic features of three sib-pairs of pathologically-confirmed progressive supranuclear palsy (PSP).
Methods: We searched the Mayo Clinic neurodegenerative diseases brain bank for cases of PSP in which more than one family member had pathologically-confirmed PSP. Clinical and pathological data were reviewed and all individuals were screened for mutations in *MAPT*, by sequencing exons 1, 7, and 9–13.
Results: We identified three sib-pairs of pathologically-confirmed PSP. Sufficient information was available to suggest an autosomal dominant inheritance in two. The mean age at symptom onset was 41 years in one pair, and 76 years in the other two. The young onset pair had a p.S285R mutation in *MAPT*, but no mutations were detected in the other two.
Conclusions: All sib-pairs had typical pathological features of PSP; however, the age at onset of the sib-pair with *MAPT* mutation was significantly younger than sporadic PSP. Future studies are warranted to identify a possible genetic basis for PSP associated with late onset and typical PSP pathology.

1. Introduction

Progressive supranuclear palsy (PSP) is a relatively rare neurodegenerative disorder [1]. Patients with PSP typically present with an akinetic-rigid syndrome, supranuclear gaze palsy, cognitive impairment, and falling that is present at the onset of their illness [2]. Pathological hallmarks are neurofibrillary tangles, coiled bodies, tufted astrocytes, and neuropil threads immunoreactive for 4-repeat tau [3]. In some familial and sporadic cases of PSP, mutations in the tau gene (*MAPT*) have been reported [4–7] of which only three cases fulfilled the pathological criteria for PSP [7–9].

Here, we describe three sib-pairs with pathologically-confirmed PSP, including one pair with a tau p.S285R substitution previously identified as a probable *de novo* mutation in a Japanese 46-year-old man with clinically probable PSP [6]. We describe the clinical and pathologic features of three sib-pairs of pathologically-confirmed PSP and review the literature on *MAPT* mutations presenting with a PSP clinical syndrome.

2. Methods

2.1. Genealogical and clinical studies

We extracted clinical information, including cardinal clinical features of PSP, from the available medical records and constructed pedigrees.

2.2. Pathologic analysis

All cases had a standardized neuropathologic evaluation as part of the normal operating procedures of the brain bank for neurodegenerative diseases at the Mayo Clinic Jacksonville. All cases had semiquantitative assessment of neuronal and glial tau pathology with immunohistochemistry for phospho-tau (CP-13; mouse IgG1, 1:1000), screening for other pathologies with routine histologic methods, and thioflavin-S fluorescent microscopy and immunohistochemistry.

2.3. MAPT mutation screening

Genomic DNA was isolated from brain tissue using the Gentra Puregene kit (Qiagen, Venlo, Netherlands). Polymerase chain reactions (PCR) were performed using primer sets designed to flank intronic sequences of exons 1, 7, and 9 through

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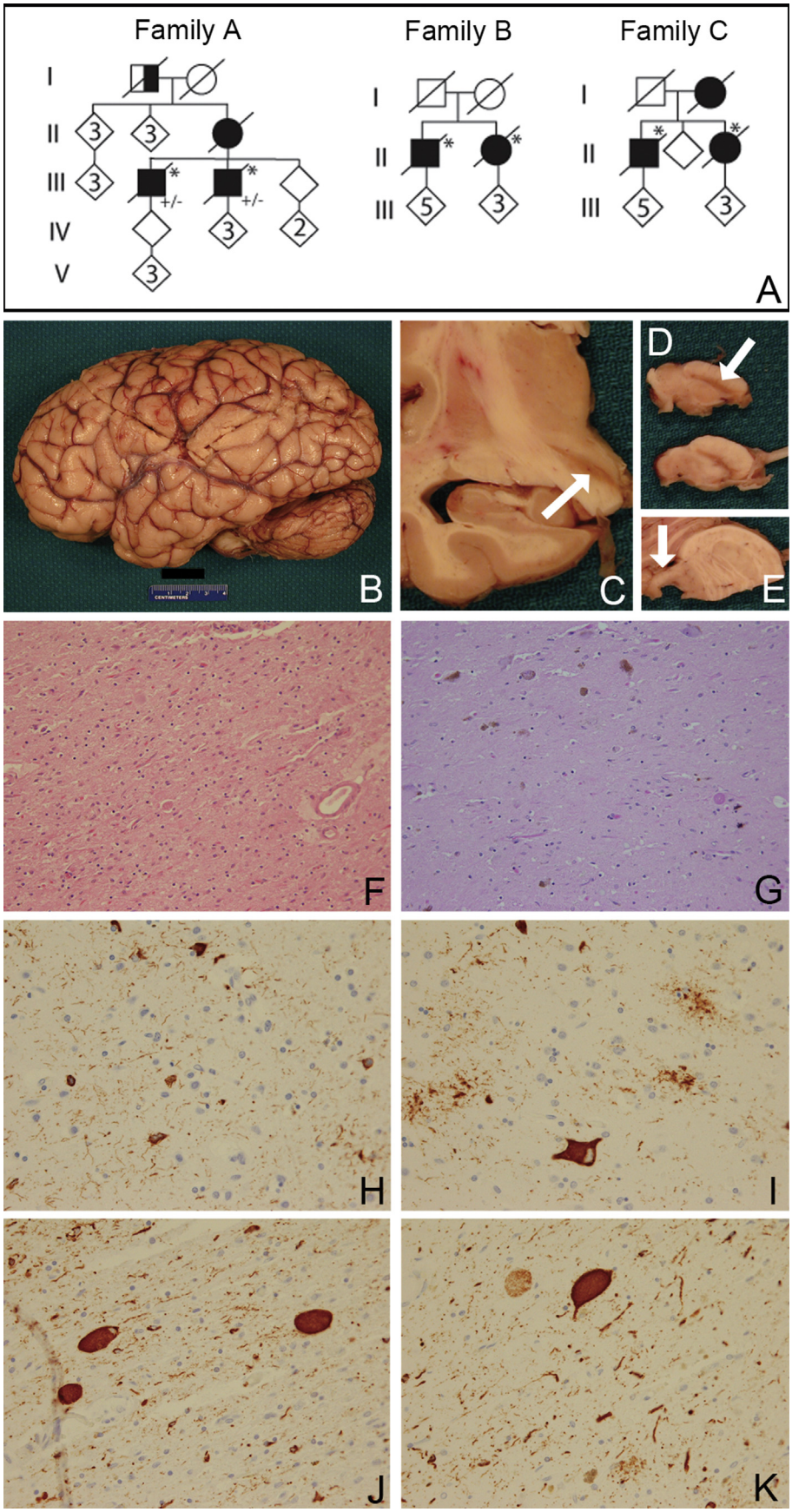

Fig. 1. Pedigrees of three sib-pairs of progressive supranuclear palsy (A), and pathological features of Case 2 (B–K). Standard pedigree symbols were used. Round symbols indicate females; squares indicate males; and diagonal lines indicate that the individual is deceased. Diamonds were used to disguise gender. +/– indicates heterozygous S285R *MAPT*