ELSEVIER

Neurobiology of Aging 33 (2012) 834.e1–834.e6

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

New mutations in *MAPT* gene causing frontotemporal lobar degeneration: biochemical and structural characterization

Giacomina Rossi[a,*], Antonio Bastone[b], Elena Piccoli[a], Giulia Mazzoleni[a], Michela Morbin[a], Andrea Uggetti[a], Giorgio Giaccone[a], Sarah Sperber[c], Marten Beeg[b], Mario Salmona[b], Fabrizio Tagliavini[a]

[a] *Division of Neuropathology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy*
[b] *Department of Molecular Biochemistry and Pharmacology, Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy*
[c] *Division of Neurology, Azienda Ospedaliera della Provincia di Lodi, Lodi, Italy*

Received 30 March 2011; received in revised form 4 August 2011; accepted 15 August 2011

Abstract

Frontotemporal lobar degeneration (FTLD) can be sporadic or familial. The genes encoding the microtubule-associated protein tau (*MAPT*) and progranulin (*GRN*) are the most relevant genes so far known causing the hereditary forms. Following genetic screening of patients affected by FTLD, we identified 2 new *MAPT* mutations, P364S and G366R, the former in a sporadic case. In the study we report the clinical and genetic features of the patients carrying these mutations, and the functional effects of the mutations, analyzed in vitro in order to investigate their pathogenic character. Both mutations resulted in reduced ability of tau to promote microtubule polymerization; the P364S protein variant also showed a high propensity to aggregate into filaments. These results suggest a high probability that these mutations are pathogenic. Our findings highlight the importance of genetic analysis also in sporadic forms of FTLD, and the role of in vitro studies to evaluate the pathologic features of new mutations.
© 2012 Elsevier Inc. All rights reserved.

Keywords: Frontotemporal lobar degeneration; Microtubule-associated protein tau; *MAPT*; Mutation; Sporadic; Microtubules; Oligomers; Amyloid fibrils

1. Introduction

Frontotemporal lobar degeneration (FTLD) includes a group of progressive degenerative disorders clinically characterized by behavioral changes and cognitive impairment. Three main phenotypes can be distinguished: frontotemporal dementia (FTD), primary progressive aphasia, and semantic dementia. A number of related diseases with extrapyramidal and/or motor component partially overlaps with FTLD, namely corticobasal syndrome, progressive supranuclear palsy, and motoneuron disease. Hereditary forms represent 20%–30% of all FTLD cases and up to 25% of them are caused by mutations in two major genes coding for microtubule-associated protein tau (*MAPT*) and progranulin (*GRN*) (Rademakers and Rovelet-Lecrux, 2009; van Swieten and Heutink, 2008).

The patients carrying *MAPT* mutations are pathologically characterized by deposition of filamentous tau inclusions in neuronal and glial cells, leading to neurodegeneration. The mutations have an autosomal dominant pattern of inheritance and their pathogenesis can be ascribed to two mechanisms: (1) reduced ability of tau to interact with microtubules, often associated with increased propensity to aggregate into abnormal filaments (missense mutations), and (2) perturbation of the normal ratio of tau isoforms, favoring aggregation (splicing mutations) (van Swieten and Spillantini, 2007). Presently, about 40 mutations have been reported (www.molgen.ua.ac.be/FTDmutations).

In this report, we describe two patients with FTLD carrying new mutations in *MAPT* gene clustered in the Pro-

* Corresponding author at: Division of Neuropathology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Via Celoria 11, 20133 Milan, Italy. Tel.: +39 02 2394 4582; fax: +39 02 2394 2101
E-mail address: grossi@istituto-besta.it (G. Rossi).

0197-4580/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.neurobiolaging.2011.08.008

Gly-Gly-Gly motif of the fourth microtubule binding repeat (R4) (van Swieten and Spillantini, 2007). We performed in vitro functional experiments with recombinant mutated tau, indicating a high probability of the pathogenicity of these genetic defects.

2. Methods

In this study we did not perform any experimental treatment on human subjects.

The informed consent to genetic analysis for diagnostic and research purposes was obtained from all subjects, and the Institutional Review Board of Fondazione IRCCS Istituto Neurologico Carlo Besta was notified about this study. The Institutional Review Board considered this satisfactory and did not require further evaluation for the study.

Italian patients affected by neurodegenerative diseases of the FTLD spectrum ($n = 71$; age of onset: range, 36–80 years; mean ± SD, 57 ± 9) underwent clinical and neurological examination at the Istituto Neurologico Carlo Besta, Milan. Clinical diagnosis of FTD ($n = 37$), FTD-motoneuron disease ($n = 8$) (Neary et al., 1998), primary progressive aphasia ($n = 11$) (Mesulam, 1982), corticobasal syndrome ($n = 9$) (Riley et al., 1990), and progressive supranuclear palsy ($n = 6$) (Litvan et al., 1996) was made according to international guidelines. Genetic screening for *MAPT* was performed and two FTD patients carrying new *MAPT* mutations were identified. We report in detail their clinical data and pedigrees (family EP and family DM).

To investigate the presence of these new mutations in Italian control subjects, we recruited 100 healthy individuals (age: range, 22–73 years; mean ± SD, 41 ± 12), 149 patients with possible or probable Creutzfeldt-Jakob disease (age of onset: range, 28–86; mean ± SD, 64 ± 13) (Zerr et al., 2009), 27 with mutation in *PRNP* gene (age of onset: range, 33–77; mean ± SD, 61 ± 11), 117 with probable Alzheimer's disease (age at onset: range, 45–84; mean ± SD, 62 ± 10) (Dubois et al., 2007), and 7 with mutation in *APP* or *PS1* genes (age of onset: range, 42–79; mean ± SD, 58 ± 12).

2.1. Case reports

2.1.1. Family EP

At age 47 the proband (II-2, Fig. 1) presented with memory loss and mood deflection after his divorce. Paroxetine treatment was started with beneficial effects on the depressive state. Magnetic resonance imaging (MRI) showed asymmetrical cerebral atrophy with ventricular enlargement and signal abnormalities in the periventricular white matter (both changes more evident on the left side) (Fig. 2A). The Mini Mental State Examination (MMSE) score was 18/30. As disease progressed, apathy, disinhibition, inappropriate eating behavior, loss of money recognition skill, and reduced personal care appeared. At age 52, a neuropsychological examination confirmed the severe memory impairment and revealed constructive apraxia, agraphia, and severe attention deficits.

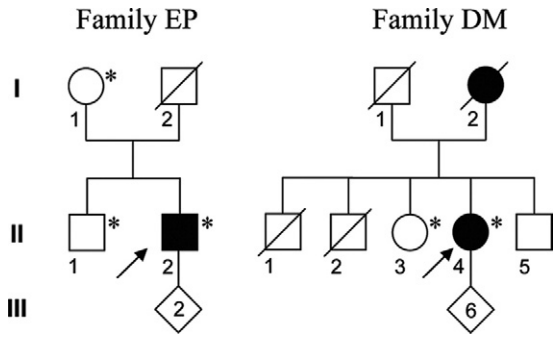

Fig. 1. Pedigrees of the families EP and DM. Closed symbols indicate affected subjects, arrows the probands, and diagonal lines the deceased. * Subjects who underwent genetic analysis.

The father of the proband (I-2) died at age 75, from lung cancer. The mother (I-1) is alive, aged 76, without cognitive or behavioral disturbances.

Inquiry into the proband's paternal and maternal pedigrees disclosed absence of dementia in all five siblings of the father and in his parents, as well as in all six siblings of the mother and in her parents.

2.1.2. Family DM

At age 52, the proband (II-4, Fig. 1) began to have bizarre behavior (she threw objects and food away from the window, she tried to climb the roof of her house) and showed modification of her personality, without apparent deficits in daily housework. At age 57 apathy and lack of interest in personal and social activities were evident, associated with occasional aggressive behaviors. At age 61 she was admitted to the hospital for severe memory and language disturbances and dysarthria, apraxia, clumsiness in walking, mild rigidity and bradykinesia, dysmetria, dysphagia, and impaired ocular movements (slight upward vertical gaze palsy). Mini Mental State Examination score was 9/30. MRI revealed moderate to severe symmetrical sovratentorial cerebral atrophy, predominantly involving the frontal lobe, with venticular enlargement (Fig. 2B).

The mother of the proband (I-2) died at age 55, after an 8-year history of dementia with prominent behavioral disturbances; unfortunately, we do not have further information about the rest of her family nor about the proband's paternal pedigree.

2.2. Genetic analysis

After informed consent, genomic DNA was extracted from peripheral blood lymphocytes of the following subjects: the 71 FTLD, including the probands of families EP and DM; the mother (I-1) and the brother (II-1) of family EP's proband; the sister (II-3) of family DM's proband; all control subjects. Sequence analysis of exons 9–13 of *MAPT* (Poorkaj et al., 1998) was performed on the 71 FTLD subjects, while on the relatives of the probands and control

Download English Version:

https://daneshyari.com/en/article/6809533

Download Persian Version:

https://daneshyari.com/article/6809533

Daneshyari.com