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Frontotemporal dementia and parkinsonism linked to chromosome 17 - the first Polish family

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Abstract

Background—Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) is a neurodegenerative disorder with various clinical phenotypes. We present the first Central-Eastern European family (Gdansk Family) with FTDP-17 due to a P301L mutation in *MAPT*.

Methods—We have studied a family consisting of 82 family members, 39 of whom were genetically evaluated. The proband and her affected brother underwent detailed clinical and neuropsychological examinations.

Results—P301L mutation in *MAPT* was identified in two affected and five asymptomatic family members. New features included hemispatial neglect and unilateral resting tremor not previously reported for P301L *MAPT* mutation. Low blood folic acid levels were also detected.

Conclusions—Our report suggests that FTDP-17 affects patients worldwide, but due to its heterogenous clinical presentation remains underrecognized.

Keywords

FTDP-17; *MAPT*; P301L mutation

Introduction

Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) is characterized by behavioral and cognitive abnormalities accompanied by parkinsonism [1]. Pathogenic mutations in the genes located on chromosome 17q21-22, encoding the microtubule-associated protein tau (*MAPT*) and progranulin (*GRN*), were identified as a cause of FTDP-17 [2–3]. The extended *MAPT* genotype is reported as a predisposing factor for specific initial symptoms of FTDP-17. The H1/H1 haplotype has been associated with initial parkinsonian phenotype, while the H1/H2 haplotype with frontotemporal dementia

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[4]. The P301L mutation is one of the most prevalent pathogenic *MAPT* mutations associated with FTDP-17 [5]. We report a large family with new clinical manifestation of the P301L mutation.

Patients and methods

The affected siblings: patient III.16 and patient III.15 (Fig.1) underwent a detailed clinical, neuroimaging and neuropsychological assessment. Blood samples for genetic analysis were obtained from family members (n=39). Neurological examination was performed in all asymptomatic gene carriers (n=5) and non-carriers (n=17). Data on other family members was collected by interviews and reviewing the available medical records of deceased patients. The study protocol was approved by the Ethic Committee of the Medical University of Gdansk and all patients provided written consents to participate in all procedures.

Results

The pedigree consists of 82 family members over 4 generations (Fig.1). Two affected and five presymptomatic individuals were mutation carriers for P301L in *MAPT*.

The proband, a 57- year-old woman (III.16), presented with behavioral abnormalities since the age of 51. Parkinsonism started after five years of disease's duration. Neuropsychological assessment at the age of 57 revealed severe dementia with prominent dysexecutive symptoms, anomia, high distractibility and mild visuospatial disturbance. She died at the age of 58.

The proband's brother (III.15) was diagnosed at the age of 58, with a 10 year-history of depression. Unilateral resting tremor as the initial symptom of parkinsonism started at the age of 55 and a diagnosis of Parkinson's disease (PD) was established. He was administered levodopa with benserazide with initially very good response. At the time of FTDP-17 diagnosis he presented with prominent working memory impairment and dysexecutive symptoms. Subsequently, unilateral neglect appeared [6].

Sequencing analysis of *MAPT* and *GRN* identified the c.1907C>T mutation in exon 10 of *MAPT*. Both patients were homozygous for the extended H1 *MAPT* haplotype.

Structural brain imaging including computed tomography and magnetic resonance imaging showed diffuse cerebral atrophy with frontotemporal predominance (Fig.2). Right-sided hypoperfusion of the frontal and temporal lobes was shown on the single photon emission computed tomography. Low blood folic acid levels were detected: 3.6 ng/ml in the proband and 1.68 ng/ml in the brother (normal laboratory range: 4.2–19.9 ng/ml). Neurological examination performed in all asymptomatic gene carriers (n= 5, age range: 29–34 years) revealed mild rigidity in the left extremities in a 29-year-old woman (IV.13). We found a co-occurrence of early onset multiple sclerosis (MS) (10/82) and psoriasis (3/82) in the Gdansk Family.

Discussion

We present the first Central-Eastern European family with genetically confirmed FTDP-17 carrying the P301L mutation in *MAPT*. Although the P301L mutation is the most common and well described *MAPT* mutation, the affected members from the Gdansk Family presented with hemispatial neglect and unilateral resting tremor, all of them not previously reported for P301L *MAPT* mutation [6–11]. We have also found low blood folate levels not related to poor diet or alcohol abuse. Coincidence of early onset MS (10/82) and psoriasis

(3/82) in the presented family is notable. These disorders sometimes run in families, but they usually do not show Mendelian inheritance and are associated with both genetic susceptibility and environmental exposure. Psoriasis in some families is inherited as an autosomal dominant trait and loci at chromosome 17q25 have been identified [12]. A possible role of chromosome 17 inversion polymorphism in genetic susceptibility to MS was also studied [13]. This first report on FTDP-17 in Central-Eastern Europe suggest that disease occurs world-wide and remains under recognized.

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References

1. Foster NL, Wilhelmsen K, Sima AAF, et al. Frontotemporal dementia and parkinsonism linked to chromosome 17: A consensus conference. Annals of Neurology. 1997; 41:706–715. [PubMed: 9189031]
2. Poorkaj P, Bird TD, Wijsman E, et al. Tau is a candidate gene for chromosome 17 frontotemporal dementia. Annals of Neurology. 1998; 43:815–825. [PubMed: 9629852]
3. Baker M, Mackenzie IR, Pickering-Brown SM, et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature. 2006; 442:916–919. [PubMed: 16862116]
4. Baba Y, Tsuboi Y, Baker MC, et al. The effect of tau genotype on clinical features in FTDP-17. Parkinsonism and Related Disorders. 2005; 11:205–208. [PubMed: 15878580]
5. Reed LA, Wszolek ZK, Hutton M. Phenotypic correlations in FTDP-17. Neurobiology of Aging. 2001; 22:89–107. [PubMed: 11164280]
6. Sitek EJ, Narozanska E, Slawek J, et al. Unilateral neglect in a patient diagnosed with frontotemporal dementia and parkinsonism linked to chromosome 17. Acta Neuropsychiatrica. 2009; 21:4.
7. Bird TD, Nochlin D, Poorkaj P, et al. A clinical pathological comparison of three families with frontotemporal dementia and identical mutations in the tau gene (P301L). Brain. 1999; 122:741–756. [PubMed: 10219785]
8. Wszolek ZK, Lynch T, Wilhelmsen KC. 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 and Related Disorders. 1997; 3:67–76. [PubMed: 18591058]
9. Bird TD, Nochlin D, Poorkaj P, et al. Clinical pathological comparison of three families with frontotemporal dementia and identical mutations in the tau gene (P301L). Brain. 1999; 122:741–756. [PubMed: 10219785]
10. Pal PK, Wszolek ZK, Uitti R, et al. Positron emission tomography of dopamine pathways in familial parkinsonian syndromes. Parkinsonism and Related Disorders. 2001; 8:51–56. [PubMed: 11472880]
11. Wszolek ZK, Markopoulou K. Molecular genetics of familial parkinsonism. Parkinsonism and Related Disorders. 1999; 5:145–155. [PubMed: 18591133]
12. Bhalearo J, Bowcock AM. The genetics of psoriasis: a complex disorder of the skin and immune system. Human Molecular Genetics. 1998; 7:1537–1545. [PubMed: 9735374]
13. Goris A, Maranian M, Walton A, et al. No evidence for association of a European-specific chromosome 17 inversion with multiple sclerosis. European Journal of Human Genetics. 2006; 14:1064. [PubMed: 16736032]

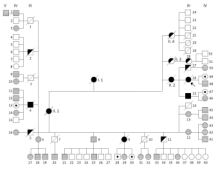

Figure 1.

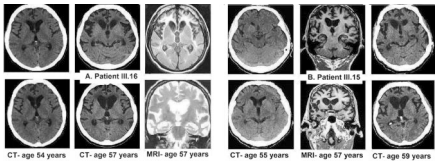

Figure 2.