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Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 1 (2015) 481-486

Alzheimer's & Dementia

Genetics

# Semantic and nonfluent aphasic variants, secondarily associated with amyotrophic lateral sclerosis, are predominant frontotemporal lobar degeneration phenotypes in *TBK1* carriers

Paola Caroppo[a,b,1], Agnès Camuzat[a,1], Anne De Septenville[a], Philippe Couratier[c], Lucette Lacomblez[d,e,f,g], Sophie Auriacombe[h], Olivier Flabeau[h], Ludmila Jornéa[i], Frederic Blanc[j,k], François Sellal[l,m], Benjamin Cretin[j,k], Vincent Meininger[d], Marie-Céline Fleury[j,k], Philippe Couarch[i], Bruno Dubois[a,d,n], Alexis Brice[a,d,n,o], Isabelle Le Ber[a,d,n,*]

[a]*Institut du Cerveau et de la Moelle épinière (ICM), CNRS UMR 7225, INSERM U 1127, Sorbonne Universités, Université Pierre et Marie, Univ Paris 06, UPMC-P6 UMR S 1127 - Hôpital Pitié-Salpêtrière, Paris, France*

[b]*Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Fondazione Istituto Neurologico "C. Besta," Milan, Italy*

[c]*Service de Neurologie, CHU Dupuytren, Limoges, France*

[d]*APHP, Département des Maladies du Système Nerveux, Hôpital de la Salpêtrière, Paris, France*

[e]*Sorbonne Universités, UPMC Univ Paris 6, Pharmacologie, Paris, France*

[f]*INSERM, UMR-S 1146, Laboratoire d'Imagerie Médicale, Paris, France*

[g]*INSERM, Centre d'Investigation Clinique, CIC-1422, Paris, France*

[h]*Centre Mémoire de Ressource et de Recherche D'Aquitaine, Institut des Maladies Neurodégénératives Clinique (IMNc), Bordeaux, France*

[i]*DNA and cell bank, Institut du Cerveau et de la Moelle épinière (ICM), CNRS UMR 7225, INSERM U 1127, Sorbonne Universités, Université Pierre et Marie, Univ Paris 06, UPMC-P6 UMR S 1127 - Hôpital Pitié-Salpêtrière, Paris, France*

[j]*Unité de Neuropsychologie, CMRR, Service de Neurologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France*

[k]*Équipe IMIS/Neurocrypto, Fédération de Médecine Translationnelle de Strasbourg (FMTS), Laboratoire ICube, Université de Strasbourg et CNRS, Strasbourg, France*

[l]*Centre Mémoire, de Ressources et de Recherche d'Alsace, Strasbourg, France*

[m]*Service de Neurologie, Hospices Civils de Colmar, Colmar, France*

[n]*Centre de Référence des Démences Rares, AP-HP, Hôpital de la Pitié-Salpêtrière, Paris, France*

[o]*Département de Génétique et Cytogénétique, Unité Fonctionnelle de Génétique Clinique, AP-HP, Hôpital de la Pitié-Salpêtrière, Paris, France*

**Abstract**

**Introduction:** *TBK1* mutations represent a rare novel genetic cause of amyotrophic lateral sclerosis (ALS) without or with dementia. The full spectrum of *TBK1* phenotypes has not been completely defined so far.

**Methods:** We describe the clinical and neuroimaging characteristics of loss-of-function mutation carriers initially presenting with frontotemporal lobar degeneration (FTLD) phenotypes.

**Results:** Two carriers initially presented semantic variant of FTLD (svFTLD); two other developed nonfluent variant of FTLD (nfvFTLD) and corticobasal syndrome (CBS), associated with severe anterior temporal and opercular atrophy. All secondarily developed ALS.

**Discussion:** This study enlarges the phenotypic spectrum of *TBK1* mutations, including svFTLD and nfvFTLD/CBS, not reported so far. Aphasic presentations seem to be more evocative of *TBK1* genotype than behavioral variant of FTLD, and *TBK1* should be analyzed in patients with isolated FTLD at onset, particularly in rare aphasic cases secondarily associated with ALS.

The authors report no conflicts of interest.

[1]These authors contributed equally to this work.

*Corresponding author. Tel.: 00-33-1-57-27-46-82; Fax: 00-33-1-57-27-47-95.

E-mail address: isabelle.leber@upmc.fr

http://dx.doi.org/10.1016/j.dadm.2015.10.002

*Keywords:* *TBK1*; Frontotemporal lobar degeneration; Semantic variant FTLD; Aphasic variant FTLD; Genetics; Behavioral disorders; Amyotrophic lateral sclerosis

## 1. Introduction

Frontotemporal lobar degeneration (FTLD) defined three variants characterized by behavioral (behavioral variant of FTLD [bvFTLD]) or language disorders (semantic variant of FTLD [svFTLD] and agrammatic/nonfluent variant of FTLD [nfvFTLD]) [1,2]. Amyotrophic lateral sclerosis (ALS) and FTLD share common pathologic hallmarks and genetic etiologies, the most frequent being *C9orf72*.

Recently, *TBK1* loss-of-function mutations were identified as a rare genetic cause involved in 0.5%–4% of ALS [3,4]. Associated phenotypes have not been deeply defined so far. In this study, we describe in detail the clinical and neuroimaging characteristics of four loss-of-function mutation carriers initially presenting with FTLD phenotypes.

## 2. Methods

### 2.1. Patients and families

We studied four unrelated probands from unrelated French (F476, F484, and F826) and Portuguese (F500) families carrying *TBK1* loss-of-function mutations (Fig. 1A, Table 1). The mutations were identified by genetic screening of 302 unrelated FTLD patients (143 familial) including 182 probands with isolated FTLD (118 bvFTLD, 50 nfvFTLD, 2 svFTLD, and 12 progressive supranuclear paralysis) and 120 that secondarily developed ALS (113 bvFTLD, 5 nfvFTLD, and 2 svFTLD Supplementary Material). The main FTLD and ALS gene have been previously excluded in all the probands.

The proband 003 and one relative 005 of family F484 carried the p.Thr156ArgfsX6 mutation; the proband 003 of family F500 carried a p.Tyr482X mutation, that was also detected in four unaffected sibs aged 59–77 years; the probands 003 of family F826 and 003 of family F476 carried p.Gln655X and p.Leu654LysfsX18 mutations, respectively. This study was approved by the Ethics Committee of "AP-HP de Paris."

### 2.2. Clinical and neuroimaging evaluations of patients

The phenotypes have been assessed by clinical evaluations of patients, interview of caregivers, and in medical records. Brain magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT) were done in routine procedures. The diagnoses were based on international criteria [1,2,5].

## 3. Results

### 3.1. Description of FTLD phenotypes (Table 1)

Patient 003 of family F826 presented language disorders with predominant semantic deficit at age 64. Computed tomography scan revealed predominantly left, temporal anterior atrophy. At age 65, the mini-mental state examination (MMSE; 25/30), oral confrontation naming (22/40), and Boston Naming Test (13/30) scores were impaired, as well as semantic matching (35/40), famous faces recognition (13/50), and visual recognition memory scores (DMS48:42; Supplementary Table 1). He secondarily developed apathy, immotivate laughing, kleptomania, and stereotypies. At age 66, MRI revealed severe bi-temporal, predominantly left, atrophy (Fig. 1B1). He developed ALS with limb deficit and swallowing disorders, confirmed by electromyograms (EMG). He died at age 69. A parent 001 died of dementia, at age 83.

Patient 003 of family F500 presented language disorders with predominant semantic deficit, at age 68. MRI and HMPAO-SPECT showed marked bilateral, predominant marked left, anterior temporal involvement (Fig. 1B2) associated with mild frontal involvement. The oral confrontation naming (12/80, 11 semantic paraphasias), visual naming (9/18), and semantic matching (5/10) scores were impaired (Supplementary Table 1). A svFTLD was diagnosed. He secondarily presented apathy, indifference, stereotypies, right akinetic-rigid Parkinsonism, and a dysexecutive syndrome (Supplementary Table 1). At age 70, he developed spinal ALS (ALS-FRS: 24/48) and died at age 71. One sib died of ALS at age 50 (DNA was not available for this sib).

Proband 003 of family F484 developed language disorders, severe orofacial apraxia, and reduced speech evocative of agrammatic nonfluent aphasia, at age 60. The oral confrontation naming score (25/30) was impaired. Attention and memory were spared. MRI revealed bilateral but predominantly left temporal atrophy (Fig. 1B3). EMGs were normal. At age 63, he had marked apathy, gestural and eyelid apraxia, and akinetic-rigid Parkinsonism. A nonfluent aphasic subtype of corticobasal syndrome (CBS) was diagnosed. Dysarthria and swallowing disorders suggesting bulbar ALS developed later, without muscular deficit. He died at age 65. One sib (005) presented spinal ALS without behavioral changes (Frontal Behavioral Inventory score: 12/72) at age 76. No parents had neurologic disorders.