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Genetics

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

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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.

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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.

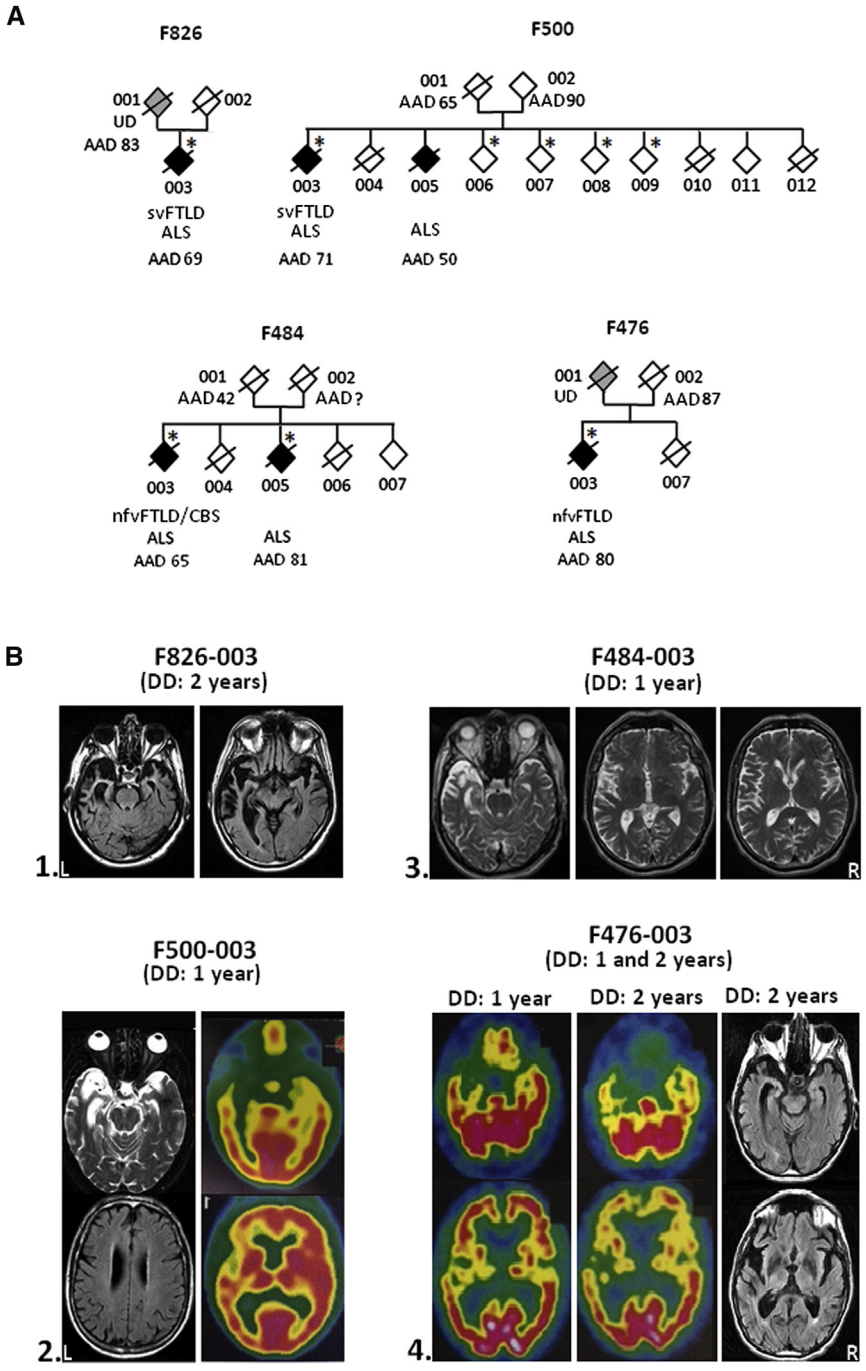

Fig. 1. (A) Pedigrees of *TBK1* families. The individuals are represented by diamonds for confidentiality. *Family members for whom DNA samples were available and carrying the mutation; black diamonds: FTLD or ALS patients; gray diamonds: unspecified dementia (UD); white diamonds: nonsymptomatic individuals. The FTLD and ALS phenotypes are indicated for the patients. Age at death (AAD) is indicated. The proband 003 of family F826 carried the heterozygous c.1963C>T (p.Gln655X) mutation. In family F500, the proband 003 and four unaffected sibs (006, 007, 008, and 009), aged 59–77 years, carried the heterozygous p.Tyr482X (c.1446T>G) mutation. In family F484, the FTLD proband, 003, and a sib with ALS (005) carried a p.Thr156ArgfsX6 (c.467_468delCA) mutation. The proband 003 of family F476 carried a p.Leu654LysfsX18 (c.1960-2A>G) mutation. (B) Neuroimaging of *TBK1* patients. (1) Patient F826-003. Axial FLAIR MRI sections, after 2 years of disease duration (at age 66), showing bilateral predominantly left anterior temporal atrophy. (2) Patient F500-003. Axial FLAIR and T2-weighted MRI sections and axial HMPAO-SPECT, after 1 year of disease duration (age 69). Marked bilateral but predominant left anterior temporal atrophy and hypoperfusion. The frontal cortex showed only mild involvement. (3). Patient F484-003. Axial T2 MRI sections at age 61 (1 year of disease duration), showing predominant left temporal anterior atrophy; frontal cortex is relatively spared. (4). Patient F476-003. Axial ECD-SPECT sections after 1 year of disease duration (at age 77) evidenced predominant left opercular and anterior temporal hypoperfusion (left). After 2 years of disease duration (at age 78), SPECT (middle) and FLAIR MRI sections (right) showing bilateral predominantly left anterior, lateral, and middle temporal regions, opercular, and bilateral frontal involvement. Abbreviations: FTLD, frontotemporal lobar degeneration; ALS, amyotrophic lateral sclerosis; MRI, magnetic resonance imaging; FLAIR, flair-attenuated inversion recovery; SPECT, single-photon emission computed tomography; DD, disease duration; L, left; R, right.

Table 1
Main clinical characteristics of probands with FTLD (F826-003, F500-003, F484-003, and F476-003) carrying *TBK1* mutations

Families	Patients	Mutations	Age at onset FTLD	First FTLD symptom	FTLD diagnosis	Late FTLD symptoms occurring during disease progression	Other symptoms	Age at onset ALS	MRI (years of disease)	SPECT (years of disease)	Age at death
F826	003 (proband)	c.1963C>T (p.Gln655X)	64	Semantic deficits	svFTLD	Apathy, immotivate laughing, kleptomania, and stereotypies	Spinal ALS	66	Predominant left anterior temporal atrophy (2)	NA	69
F500	003 (proband)	c.1446T>G (p.Tyr482X)	68	Semantic deficits	svFTLD	Apathy, indifference, and stereotypies	Spinal ALS, Park	70	Marked bilateral, predominantly left anterior temporal atrophy. Mild frontal atrophy (1)	Predominant left anterior temporal hypoperfusion (1)	71
F484	003 (proband)	c.467_468delCA (p.Thr156ArgfsX6)	60	Speech apraxia	nfvFTLD/ CBS	Apathy	Spinal ALS, Park	64	Predominant left temporal atrophy (1)	NA	65
	005 (relative)	c.467_468delCA (p.Thr156ArgfsX6)	—	—	—	—	Spinal ALS	76	NA	NA	81
F476	003 (proband)	c.1960-2A>G (p.Leu654LysfsX18)	76	Speech apraxia	nfvFTLD	Disinhibition	Spinal ALS	78	Bilateral predominantly left anterior, lateral, middle temporal and opercular atrophy. Bilateral frontal atrophy (2)	Left opercular and anterior temporal (1). Predominant left anterior, lateral and middle temporal, opercular, and bilateral frontal hypoperfusion (2)	80

Abbreviations: FTLD, frontotemporal lobar degeneration; ALS, amyotrophic lateral sclerosis; MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography; svFTLD, semantic variant of FTLD; NA, not applicable; nfvFTLD, nonfluent variant of FTLD; Park: parkinsonism; CBS, corticobasal syndrome.

Patient 003 of family F476 presented progressive speech production deficit at age 76, without orofacial muscular deficit, fasciculation, or atrophy. Speech examination evidenced severe orofacial apraxia with major difficulties in words articulation evocative of a speech apraxia. 99mTc-ethylcysteinate dimer (99mTc-ECD) SPECT evidenced predominant left opercular and anterior temporal hypoperfusion (Fig. 1B4). The clinical and neuroimaging features were consistent with nfvFTLD. EMGs were normal. He later developed disinhibition, euphoria, perseverations, imitation behaviors, and marked frontal syndrome (Frontal Assessment Battery [FAB]: 12/18; MMSE: 24/30). At age 78, he developed moderate limb weakness, enhanced reflexes, and Babinski sign. MRI and 99mTc-ECD-SPECT showed predominant left anterior, lateral, and middle temporal regions, opercular and bilateral frontal involvement (Fig. 1B4). The FAB score was 9/18. He died at age 80. The parent, 001, developed dementia and died at age 65; one sib 007 died at age 35 of "poliomyelitis."

4. Discussion

So far, *TBK1* loss-of-function mutations have been mainly reported in rare patients with ALS, isolated or secondarily associated with dementia [3,4], and in one patient only with FTLD [6], whose clinical phenotype has not been precisely described. In this study, we report the first detailed description of clinical, cognitive, and neuroimaging characteristics of four *TBK1* probands who presented inaugural FTLD phenotypes. These cases now clearly demonstrate the direct relation, not coincidental, between FTLD presentations and *TBK1* mutations.

Strikingly, none of these patients had typical bvFTLD at onset. Two initially presented semantic dementia with temporopolar atrophy, not reported so far; two other developed predominant orofacial and speech apraxia consistent with nfvFTLD at onset. One of the latter secondarily developed Parkinsonism and limb apraxia consistent with criteria of possible nfvFTLD/CBS [7]. This study, thus, shows that the *TBK1* phenotypes are larger than initially reported, including semantic dementia, speech apraxia, and nfvFTLD/CBS, and our series suggest that these phenotypes could be more frequently associated with this genotype than bvFTLD.

Interestingly, four of seven (57%) of our subset of patients with svFTLD or nfvFTLD associated with ALS carried a mutation. nfvFTLD and svFTLD are usually much more rarely associated with ALS than bvFTLD [8,9], except in *TBK1* carriers as demonstrated in this study. This is supported by the recent description of one patient carrying both *TBK1* and *OPTN* mutations who also initially developed nfvFTLD [6]. This genotype seems, therefore, rather distinct from *C9orf72*, where classic behavioral variant is largely the predominant FTLD presentation [10,11]. Neuroimaging characteristics were strikingly similar in all cases, showing predominant severe anterior temporal and opercular atrophy at onset, with only mild or moderate frontal involvement, and were well correlated with these phenotypes.

Ages at onset were variable, from 50 to 76 years in our families. A previous study indicated a high penetrance of *TBK1* mutations in ALS families [4]. Our study suggests that penetrance after the age of 70 years is lower than previously estimated because three carriers of family F500 were unaffected at age 70–77. If confirmed in larger cohorts, this result will have important implications for genetic counseling.

Finally, this study will have important impact for clinical practice. It enlarges the phenotypic spectrum of the disease and contributes to define neuroimaging characteristics associated with this genotype. Both FTLD and ALS phenotypes can be associated with *TBK1* mutations, showing no clear correlation between the phenotype and genotype. The interfamilial and intrafamilial phenotypic variability characterizing *TBK1* carriers is not explained by the mutations, all producing haploinsufficiency as a common effect.

Importantly, aphasic presentations could be more characteristic of *TBK1* mutations than the bvFTLD, although this observation should be confirmed in larger series of patients with sv/nfvFTLD with ALS. This study, thus, suggests that *TBK1* mutations should be also searched for in patients presenting with isolated FTLD at onset, particularly in rare aphasic cases who secondarily develop ALS.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.dadm.2015.10.002.

RESEARCH IN CONTEXT

1. Systematic review: *TBK1* mutations are a rare novel genetic cause of amyotrophic lateral sclerosis (ALS) without or with dementia, but the full spectrum of *TBK1* phenotypes has not been completely defined so far. We describe in detail the clinical characteristics of *TBK1* mutation carriers presenting with isolated frontotemporal lobar degeneration (FTLD) at onset.
2. Interpretation: All patients presented aphasic and semantic disorders at onset, a presentation not reported so far. This study thus contributes to enlarge the phenotypic spectrum of *TBK1* mutations, and suggest that this presentation could be evocative of this genotype, more than the behavioral variant of FTLD.
3. Future directions: These findings will have important impact for clinical practice, showing that the *TBK1* gene should be analyzed not only in ALS but also in patients who initially present with isolated FTLD at onset, particularly in rare aphasic cases that secondarily develop ALS.

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