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Clinical phenotypes and radiological findings in frontotemporal dementia related to TARDBP mutations

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Abstract

It has been shown that different genes could be associated with distinctive clinical and radiological phenotypes of FTD. TARDBP gene has been described worldwide in few cases of FTD so its phenotype is still unclear. The objective is to study the clinical and radiological characteristics of TARDBP-related FTD. In the present study, we report clinical, neuropsychological and radiological features of five new Sardinian non-related cases of FTD carriers of the p.A382T TARDBP mutation. Furthermore, we reviewed non-related FTD cases with TARDBP mutations previously described in literature. The p.A382T missense mutation of TARDBP was present in the 21.7 % of familial cases of our FTD cohort (5/23) and in no one of the sporadic patients. 3 of 5 patients showed a temporal variant FTD and 4/5 a predominant temporal involvement at MRI. The review of the literature of FTD cases with TARDBP mutations showed that in 5 of 16 cases, the clinical phenotype was consistent with temporal variant of FTD or semantic dementia (31 %) and in 7 of 16 cases neuroimaging showed predominant temporal lobe involvement (43.7 %). Our study further supports the pathogenetic role of TARDBP mutations in pure FTD and in the full spectrum of FTD/ALS. The presence of a predominant temporal lobe involvement in a high percentage of FTD mutated patients with a peculiar clinical pattern could be useful in the differential diagnosis with other forms of dementia/FTD both sporadic and familial.

Keywords TARDBP Frontotemporal dementia Temporal lobe

Introduction

Frontotemporal dementia (FTD) includes three main clinical variant: behavioral variant (bvFTD), semantic dementia (SD) and progressive non-fluent aphasia (PNFA) [*1*]. The clinical manifestations largely depend on the different anatomical distribution of neuronal dysfunction and pathology. As a consequence, it is possible to distinguish different subtypes of FTD according to the clinical and radiological characteristics like predominant frontal or temporal involvement or symmetrical versus lateralized pattern [*2*]. The temporal

variant of FTD encompasses forms with predominant behavioral symptoms and SD with prominent verbal impairment if left lateralized and with progressive prosopagnosia if right lateralized. These subtypes of FTD are characterized by a prominent temporal anatomic involvement that can be shown with structural or functional neuroimaging [2–4]. Around a third to a half of FTD patients have a family history, although heritability varies across the different clinical subtypes [5]. BvFTD has been reported as the most heritable form, while familiarity in SD has been rarely described [6]. Mutations of various genes have been associated with FTD with variable frequency in different populations. The most commonly identified genes are*C9ORF72*, progranulin (PGRN) and microtubule-associated protein tau (MAPT), followed by other more rare genes such as valosin-containing protein (VCP), chromatin-modifying protein 2B (CHMP2B), and fused in sarcoma (FUS) [5]. It has been shown that different genes could be associated with distinctive clinical and radiological phenotypes of FTD [5] and particularly some of these genes cover the full spectrum of the continuum amyotrophic lateral sclerosis (ALS)/FTD. TARDBP gene mutations have been described worldwide in few cases of sporadic and familial ALS and rarely in FTD, FTD-ALS and ALS-FTD [7–10]. The clinical and radiological phenotype of FTD TARDBP related is still unclear, probably due to the low number of cases reported.
In the present study, we report clinical, neuropsychological and radiological features of five Sardinian non-related cases of FTD carriers of the p.A382T TARDBP mutation. Furthermore, we reviewed non-related FTD cases with TARDBP mutations previously described in the literature.

Materials and methods

TARDBP-mutated cases from our FTD cohort

From our series of 65 Sardinian FTD patients meeting Neary's criteria for FTD [1] (42 sporadic and 23 familial), 5 were found to carry the p.A382T missense mutation of the TARDBP gene. These patients underwent an extensive neuropsychological and language examination. Behavioral disturbances were evaluated with the neuropsychiatric inventory (NPI) [11]. All patients underwent MRI 1.5 T and 4 of them underwent also perfusion single photon emission computed tomography (SPECT) with ^{99}Tc- ethylene cystine dimer (ECD) or with ^{99}Tc-HMPAO. Cases were defined as familial when a first-degree relative with FTD and/or ALS was found in the familial history [12]. No one of these cases has been previously described.

Review of the literature

Non-related FTD cases with TARDBP mutations previously described in literature were reviewed. Cases reported in clinical series but not described in details, carriers of TARDBP mutation in homozygosis or with double mutations, cases with mutations of uncertain pathogenicity were excluded.

Genetic screening

p.A382T TARDBP-mutated patients in our cohort underwent also genetic analysis for other TARDBP mutations in Exon 6, *C9ORF72*, *PGRN* (all exons), and *MAPT* (all exons). The technique used in our laboratory for the genetic analysis of these mutations in the TARDBP and C9ORF72 genes was previously described [13, 14]. All coding exons of PGRN and MAPT have been PCR amplified, sequenced using the Big-Dye Terminator v3.1 sequencing kit (Applied Biosystems Inc.), and run on an ABIprism 3500xL genetic analyzer (Applied Biosystems Inc.).

Standard protocol approvals

The study has been approved by the Ethical Committee of our institution and in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.
Patients provided written informant consent.

Results

Genetic analysis

C9ORF72, MAPT, PGRN and other mutations in exon 6 of the TARDBP gene were excluded in the five patients with the heterozygous p.A382T missense mutation. All cases were familial and apparently unrelated (4 patients had a familial history of FTD and one of ALS). The mean age at onset was 50.8 years (range 38–67 years).
Family trees of our five patients are described in Fig. 1.

Detailed case descriptions

Case 1 (Family A)

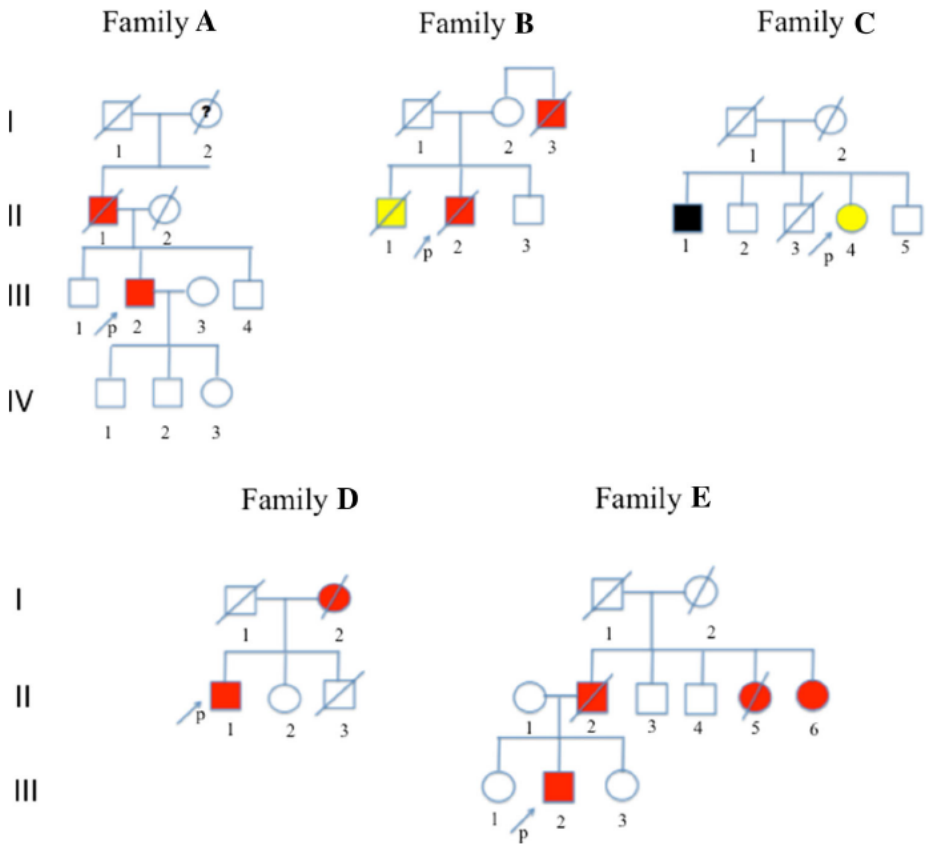
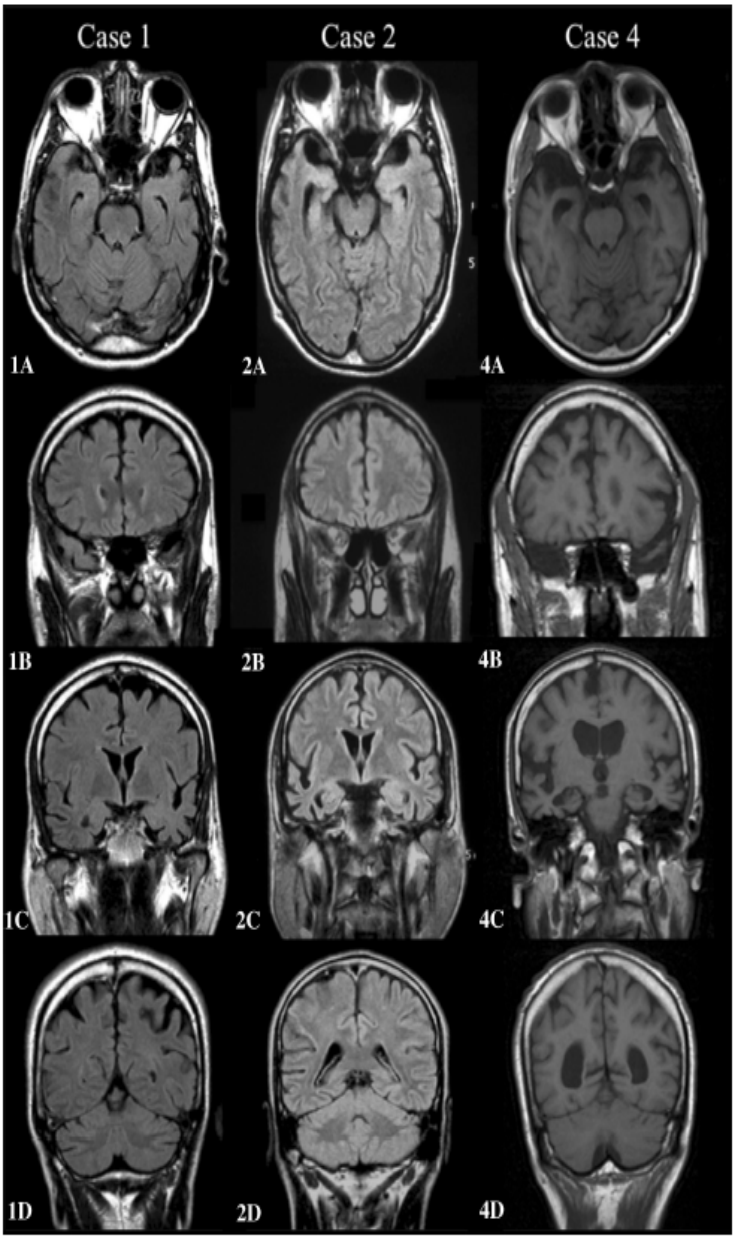


Fig. 1 Pedigrees of families a–e. *Squares* indicate males; *circles* females; *diagonal lines* deceased; *p* proband; *red* indicates patients with FTD; *yellow* FTD/ALS; *black* ALS; ? possible affected

A right-handed man developed at the age of 38 years behavioral disturbances with irritability and sometimes aggressiveness, social withdrawal, fixed ideas and obsessive repetitive behaviors mainly regarding his wife and secondary his body aspect, leading him to spend the most part of the day in body-building activities and to use testosterone and anabolic steroids.
As in the first phase, the patient presented only psychiatric symptoms he was seen by psychiatrists and the diagnosis of borderline personality disorder was made. After 3 years, when anomia for proper and common names and impairment in instrumental activity in life appeared, the patient was seen in our neurological unit. In this phase of the disease, the patient also showed anxiety, agitation, akathisia, insomnia, repetitive behaviors, disinhibition, hypersexuality, dietetic restriction and social cognition impairment. Pharmacological therapy with risperidone 4 mg was administered with partial response. Neuropsychological evaluation showed marked deficit in verbal semantic memory, impairment in naming nouns and markedly verbs, and mild executive dysfunction. There were not troubles in grammatical

comprehension tasks and sentence repetition. Speech apraxia was absent. In the personal medical history, some difficulties in learning, writing and reading at school were recorded. In the family history, we found the father affected at the age of 37 by dementia with predominant behavioral disorders and progressive language disorder. The grandmother on the paternal line developed at the age of 71 years a progressive motor impairment with muscular hypotrophy. Two child of the patients are affected by developmental dyslexia associated with impulse control disorder in the youngest (Fig. 1). Brain MRI showed moderate bitemporal atrophy predominant in the left side (Fig. 2). Brain SPECT demonstrated bilateral frontotemporoparietal hypoperfusion prevalent in the left regions and in temporal lobes (Fig. 3).



◀**Fig. 2** FLAIR (cases 1 and 2) and T1-weighted (case 4) brain MRI images. Case 1 showed moderate temporal lobes atrophy with major involvement of the superior temporal gyrus (1**a**) middle and inferior temporal gyrus and enlargement of the lateral scissure (1**b**) on the *left side*. Mild parietal atrophy was also present (1**d**). Frontal (1**b**, **c**) cortices are relatively preserved. In case 2, we found bilateral temporal lobes atrophy with bilateral involvement of the superior temporal gyrus and the middle, inferior temporal gyrus and the hippocampus on the *right side*, associated with enlargement of the lateral fissure. Frontal (2**b**, **c**) and parietal (2**d**) cortices were relatively preserved. In case 4, severe bilateral temporal atrophy predominant on the *right regions* was present, involving the superior, inferior and middle temporal gyri, hippocampi and amygdala. In this case, there was also mild involvement of superior frontal gyrus (4**b**, **c**), superior parietal gyrus (4**d**) with periventricular atrophy

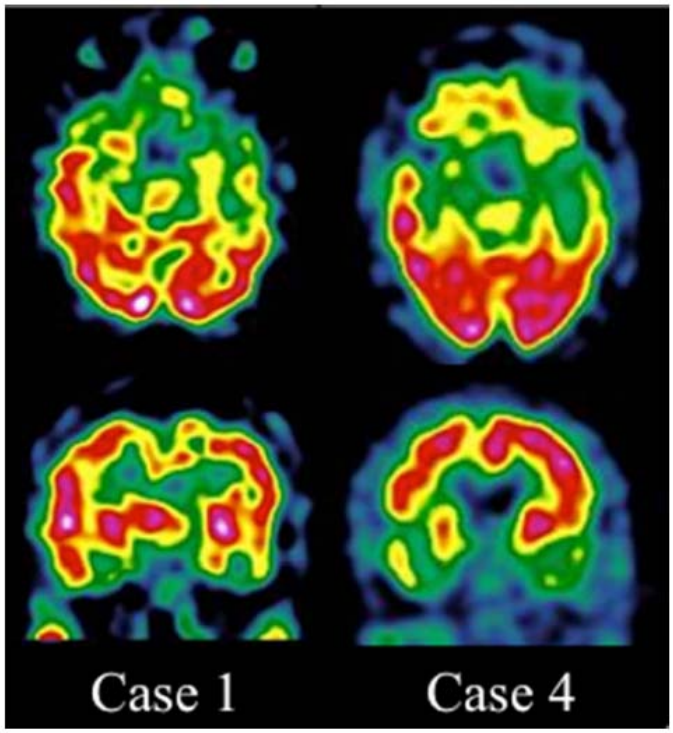


Fig. 3 Brain SPECT images of cases 1 and 4, showing marked bitemporal hypoperfusion

Case 2 (Family B)

A 45 years man developed irritability, aggressiveness, eating changes (dietetic restriction and intake of the same foods everyday), repetitive and stereotyped behaviors, fixed ideas, social cognition impairment associated with a rapid and progressive language disorder characterized initially by anomia and language comprehension impairment. Agrammatism and speech apraxia were absent. The patient spent most of his time in body-building activities and going mushrooming even if he was unable to distinguish between the poisonous and edible mushrooms. After 1 year of disease, the MMSE was not administrable, and impairment in all the instrumental activities of daily living was present with linguistic abilities reduced to some repetitive words. Nevertheless, the patient was temporally oriented, and visuospatial abilities were preserved when evaluated with simple drawings copy. In his family history, we found the brother affected at the age of 49 by frontotemporal dementia with similar features and 3 years after by motor neuron disease with bulbar signs and arms' weakness. He died after 5 years of history. The mother developed cognitive impairment of uncertain type at the age of 55 years (she had a history of alcoholism). An uncle from the maternal line had a form of dementia similar to the proband at the age of 75 (Fig. 1). Brain MRI showed bitemporal atrophy (Fig. 2). The brother with FTD had similar brain MRI features. No DNA is available of the family members of this patient.

Case 3 (Family C)

A woman developed at the age of 65 years a progressive language impairment with marked anomic deficit and executive dysfunction. Brain MRI demonstrated a left frontotemporal atrophy with predominant temporal involvement. Cerebral perfusion SPECT showed left frontotemporal hypoperfusion. At the age of 70 years, she developed ALS. Her brother, who also carried the p.A382T TARDBP mutation, developed at the age of 73 years a "flail arm" variant of ALS, later associated with mild executive dysfunction (Fig. 1).

Case 4 (Family D)

The patient developed at the age of 67 a behavioral disorder characterized by repetitive artistic activities, hyperreligiosity, gambling addiction, disinhibition, irritability, eating behavior disorder and social cognition impairment. Neuropsychological evaluation showed semantic memory dysfunction in recognition and identification of celebrities and familial people. Brain MRI showed bitemporal atrophy predominant on the right side (Fig. 2). Cerebral perfusion SPECT showed bitemporal hypoperfusion (Fig. 3). His mother developed at the age of 70 a dementia with similar features (Fig. 1).

Case 5 (Family E)

The patient, who was affected by multiple sclerosis (MS) from the age of 38 years, developed 1 year after MS onset a behavioral disturbance characterized by disinhibition, apathy, fatuity, irritability with anosognosia and progressive cognitive impairment with verbal and visuospatial memory dysfunction associated with executive impairment. Brain MRI documented white matter involvement (not able to explain the cognitive impairment) and frontotemporal atrophy. Cerebral perfusion SPECT showed a frontotemporal hypoperfusion predominant on the left side. The patient met the criteria for bvFTD. History of FTD with atypical parkinsonism with autosomal dominance pattern of inheritance was documented in his family (Fig. 1). The relatives with FTD and parkinsonism were all p.A382T TARDBP mutated.
Summary of demographic and clinical characteristics of all affected cases in our families is reported in Table 1.

Table 1 Summary of demographic and clinical characteristics of all affected cases in our families

Patient n°	Gender	Clinical phenotype	Cognitive/behavioral features at onset	AOO (years)	Duration (years)	Other symptoms/ diseases
Family A						
II:1	M	bvFTD	Obsessive repetitive behaviors, aggressiveness, aphasia	37	1[a]	Absent
III:2	*M*	*bvFTD*	*Aggressiveness, obsessive repetitive behaviors, social withdrawal*	*38*	*3*	*Developmental dyslexia*
Family B						
I:3	M	bvFTD	n.a.	75	n.a	n.a.
II:1	M	bvFTD	n.a.	49	5[a]	MND
II:2	*M*	*bvFTD*	*Irritability, aggressiveness, eating changes, repetitive stereotyped behaviors, anomia and language comprehension impairment*	*45*	*1*	*Absent*
Family C						
II:1	M	ALS/ci	Executive dysfunction	73	5	Absent
II: 4	*F*	*PPA*	*Anomia*	*65*	*7*	*MND*
Family D						
I:2	F	bvFTD	n.a.	70	16[a]	Absent
II:1	*M*	*SD*	*Repetitive artistic behaviors, hyperreligiosity, disinhibition, irritability, eating changes, social cognition impairment, semantic memory dysfunction for familial people*	*67*	*6*	*Absent*
Family E						
II:2	M	bvFTD	n.a.	65	7[a]	Parkinsonism
II:5	F	bvFTD	n.a.	70	6[a]	Parkinsonism
II:6	F	bvFTD	n.a.	75	5[a]	Parkinsonism
III:2	*M*	*bv FTD*	*Disinhibition, apathy, irritability, long-term memory and executive dysfunction*	*39*	*6*	*MS*

Probands are highlighted in italic

n.a. not available, *ALS-ci* ALS-cognitive impairment

[a] Died

Discussion

We have described five new Sardinian cases of FTD associated to the TARDBP p.A382T missense mutation. Four cases had pure FTD and one case developed ALS in the later stage of the disease. Cases 1, 2 and 4 presented many similarities of symptoms and radiological findings. Common behavioral features were irritability, aggressiveness, poor flexibility, repetitive behaviors, fixed ideas, eating changes with dietetic restriction, social cognition impairment, and emotional flatness.

Cases 1 and 2 presented language impairment resembling semantic dementia and case 4 had semantic memory dysfunction for famous people. Brain MRI showed predominant temporal involvement consistent with clinical findings (Fig. 2). The first two cases were diagnosed as bitemporal variant FTD and case 4 with right temporal variant FTD. Similar cases with behavior disorder and semantic memory impairment mainly related to bilateral temporal dysfunction and damage have been described in the literature [*3*, *4*]. Case 3 had a PPA with prevalent anomia and brain MRI showing left frontotemporal atrophy predominant in temporal lobe.

The p.A382T missense mutation of TARDBP was present in the 21.7 % of familial cases of our cohort (5/23) and in no one of the sporadic patients. TARDBP mutations are considered a rare cause of FTD outsideSardinia [*15*]; however, among our patients with familial forms of FTD, this mutation has been detected in a high percentage. Similar frequency was not reported in other populations worldwide. Its high frequency in our cohort likely reflects the peculiarity of the Sardinian isolated population in which the high prevalence of the mutation indicates a founder effect, previously observed in ALS patients [*16*]. A screening of the p.A382T missense mutation of TARDBP gene was previously performed in 443 Sardinian healthy controls; the mutation was found in 5 subjects (1.13 %) [*13*]. The presence of this low percentage of TARDBP mutations in healthy controls could be explained by this founder effect and by the age-related penetrance of this mutation [*17*]; however, the high prevalence of this mutation in sporadic and familial ALS, familial FTD and atypical parkinsonism in Sardinian patients supports its pathogenicity in these diseases [*13*, *16*, *18*]. Two other cases of FTD with p.A382T TARDBP mutation have been reported with Sardinian ancestry [*19*, *20*]. In one of these cases, 18 ALS- and FTD-related genes were screened and no mutation was found, further supporting the pathogenicity of this TARDBP mutation [*20*]. In our cases, we excluded the presence of other major genes causative of FTD like *C9ORF72, PGRN,* and *MAPT*. The high difference in prevalence inSardinia of FTD and ALS cases carriers of p.A382T TARDBP mutation could be explained by the peculiar genetic characteristics of Sardinians that differ from other Europeans, including mainland Italians [*21*].

In our study, we retrospectively analyzed reported cases of FTD carriers of TARDBP mutations in literature and we found other 11 cases. Table 2 shows demographic characteristics, clinical and neuroimaging findings available for our cases (2a) and those reviewed in literature (2b). We reviewed all the cases with TARDBP mutations comprising our cases, to better understand clinical and neuroimaging profiles. Overall, ten of these cases had the p.A382T TARDBP mutation while the others where carriers of different mutations like p.G295S, p.N267S, K263E, M359V, and p.I383V [*8*, *9*, *22*–*24*].

Table 2 Clinical and neuroimaging characteristics of TARDBP patients described in the present article and in the literature (*AOO* Age of onset, *ALS bi* ALS behavioral impairment)

Authors	Case number/ gender	TARDBP mutation type	AOO (years)	Clinical variant	Familiarity for FTD/ ALS	Brain MRI	Brain perfusion SPECT	Brain PET	MN signs	Extrapyramidal signs
Article (a)										
cases described in the present article	1 M	p.A382T Exon 6	38	Bitemporal variant FTD	FTD-ALS (?)	Bitemporal atrophy	Bilateral frontotemporoparietal atrophy predominant on the left and bitemporally	na	No	No
	2 M	p.A382T Exon 6	45	Bitemporal variant FTD	FTD-ALS	Bitemporal atrophy	Na	na	No	No
	3 F	p.A382T Exon 6	65	PPA	ALS	Left Frontotemporal atrophy predominant temporal	Left frontotemporal hypoperfusion	na	Yes	No
	4 M	p.A382T Exon 6	67	Right temporal variant FTD	FTD	Predominant right temporal atrophy	Bitemporal hypoperfusion	na	No	No
	5 M	p.A382T Exon 6	39	bvFTD	FTD	Frontotemporal atrophy	Frontotemporal hypoperfusion predominant on the left	na	No	No
Literature (b)										
Benajiba et al. [8]	6 F	p.G295S Exon 6	52	bvFTD	No	na	Bilateral frontotemporal hypoperfusion	na	Yes AOO 54 years	No
	7 F	p.G295S Exon 6	59	Semantic dementia	ALS	na	Bilateral temporopolar hypoperfusion	na	Yes AOO 61 years	No
Borroni et al. [9]	8 F	p.N267S Exon 6	74	bvFTD	No	Bilateral frontotemporal atrophy	Bilateral frontal hypoperfusion	na	No	No
Kovacs et al. [22]	9 M	K263E Exon 6	35	bvFTD	No	Mesencephalic and caudate nuclei atrophy	na	na	No	Supranuclear palsy/Chorea
Chiò et al. [10]	10 F	p.A382T Exon 6	58	bvFTD	FTD and ALS	Normal	na	Frontoparietal and left caudate hypometabolism	Yes AOO58 years	No
	11 M	p.A382T Exon 6	44	bvFTD	FTD and ALS	Normal	na	Frontal and right temporal and caudate hypometabolism	Yes AOO 43 years	No
	12 F	p.A382T Exon 6	29	ALS bi	FTD and ALS	Normal	na	Left frontotemporal hypometabolism	Yes AOO 25 years	No

Table 2 continued

Authors	Case number/ gender	TARDBP mutation type	AOO (years)	Clinical variant	Familiarity for FTD/ ALS	Brain MRI	Brain perfusion SPECT	Brain PET	MN signs	Extrapyramidal signs
Bonomi et al. [23]	13 F	M359V Exon 6	74	bvFTD	No	na	na	na	No	No
Quadri et al. 2011	14 F	p.A382T Exon 6	77	bvFTD	FTD	na	na	na	No	Atypical parkinsonism AOO 76 years
Synofzik et al. [20]	15 M	p.A382T Exon 6	31	bvFTD	ALS	Predominant bitemporal atrophy	na	Bilateral frontotemporoparietal and caudate hypometabolism	No	No
Gelpi et al. [24]	16 M	p.I383V Exon 6	60	Semantic dementia	FTD (?)	Bilateral temporal atrophy L > R	Left frontotemporal hypoperfusion	na	No	No

na not available

Ten of these patients showed a bvFTD phenotype consistent with frontotemporal dysfunction. One patient was diagnosed as PPA with marked anomia (case 3, Table 2). Five cases showed a temporal variant of FTD (2 SD, 1 right temporal variant and 2 bitemporal variant FTD). Brain MRI in six of these cases demonstrated prevalent temporal atrophy (Table 2). Synofzik et al. [*20*] described a case of early-onset bvFTD caused by p.A382T TARDBP mutation in which MRI demonstrated a rapidly progressive generalized cerebral atrophy particularly pronounced bilaterally in anterior temporal lobes and the hippocampal formations (Case 15, Table 2). Benajiba et al. [*8*] reported a case of SD in which brain SPECT demonstrated bilateral temporopolar hypoperfusion (case 7, Table 2).

Taken together these data show that in 5 of 16 cases, the clinical phenotype was consistent with temporal variant of FTD or semantic dementia (31 %) and in 7 of 16 cases neuroimaging showed predominant temporal lobe involvement (43.7 %).

Considering only the cases with the p.A382T mutation, the clinical phenotype was compatible with temporal variant of FTD in 3 of 10 cases, with neuroimaging findings showing prevalent involvement of temporal regions in 5 of 10 patients. Temporal variant of FTD has been rarely reported associated with other known FTD genes. Some cases of behavioral temporal variant of FTD with *MAPT* mutations have been reported [*3*]. SD is considered the subtype of FTD less frequently reported as familial or associated to genetic mutation [*4*]. Hodges et al. [*6*] reported in a large case series of SD patients, a low familial rate between 2 and 7 %. Familial cases of semantic dementia were rarely described in patients with mutations of *MAPT, PGRN* and *C9ORF72* genes [*25*–*27*]. In contrast, TARDBP mutations seem to be associated with familial SD in a considerable percentage of cases. Among the 16 cases reported in literature with TARDBP mutations, 12 cases had familiarity for dementia (usually FTD) or ALS, including cases with temporal variant FTD. Our results suggest that in the rare cases of familial SD could be worthy a genetic screening for TARDBP mutations.

Reviewed TARDBP-mutated cases were heterogeneous for age of onset (range 29–77 years), the clinical phenotype that covered entire spectrum ALS/FTD (pure FTD in 10/16 cases) and the presence/absence of parkinsonism. This heterogeneity described even in the same familial cluster could be attributed to genetic and epigenetic factors [*20*]. Nevertheless, the presence of a predominant temporal lobe involvement

in a high percentage of patients (30–40 %) with a peculiar clinical pattern could be useful in differential diagnosis with other forms of dementia/FTD both sporadic and familial. This phenotype is not specific of p.A382T mutation of Sardinian ancestry, as it has been found also associated with p.G295S and p.I383V TARDBP mutations. These mutations are all located on the C terminal of the exon 6 and they have been found in other populations worldwide [*8*, *24*]. These data suggest a possible common pathway in the pathogenic mechanism of these mutations. Furthermore, in TARDBP-mutated FTD patients were rarely reported delusions (1/16 patients) and hallucinations (only 1/16 patients after levodopa administration), which are frequently present in FTD related to C9ORF72 [*27*].

In one of our cases, we found a familial developmental dyslexia which was present in the patient and his sons. A significantly higher frequency of learning disability in patients with PPA and their first-degree family members was previously reported and it has been hypothesized that it may constitute a risk factor for PPA [*28*]. Recently, these data has been found in the logopenic variant of PPA which is most often sustained by Alzheimer's disease pathology [*29*]. To our knowledge, there are no studies that investigate the association between genetic forms of PPA and developmental dyslexia. Whether the developmental dyslexia in our cases may be related to TARDBP mutation is uncertain and further studies are needed to clarify this issue.

Even with some limitations due to the low number of FTD cases carriers of TARDBP mutations and the few pathological data on these patients [*22*, *24*], our study further supports the pathogenetic role of this gene in FTD and in the full spectrum FTD/ALS. Further studies are necessary to confirm the neuroimaging features of these patients. Comparison with other pattern of atrophy in different genetic forms of FTD is needed. Various studies with the objective of clarifying pathogenetic mechanism of this and other FTD/ALS-related genes and to develop targeted disease-modifying therapies are underway. In that perspective, a better characterization of TARDBP-related FTD phenotype could be useful to improve diagnostic accuracy.

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Conflicts of interest The authors have no conflicts of interest.

Ethical standard The patients and their relatives gave their informed consent prior to their inclusion in the study. The study has been approved by the Ethical Committee of our institution and in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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