	1A	1C	1D	1E	1F[a]	1G	2H	3K	4L	4M	5O	6P	7Q
Gender	F	F	F	M	F	M	M	F	M	M	M	M	M
Age at onset	55	69	55	44	58	46	42	47	54	65	49	60	49
Disease duration (years)	8	10	2	10	23*	8*	11	11	5	7*	17*	8	12
Clinical diagnosis	bvFTD	bvFTD	bvFTD	bvFTD	bvFTD	svPPA	bvFTD	bvFTD	bvFTD	bvFTD	svPPA	bvFTD	bvFTD
Clinical symptoms													
Behavioral disinhibition	++	++	+	+	+	-	++	-	+	++	+	-	+
Apathy/loss of sympathy	+	+	-	+	±	+	++	+	±	±	++	+	-
Compulsivity/stereotypes	-	-	-	+	+	+	+	+	+	-	+	+	-
Hyperorality/dietary changes	+	-	-	-	+	-	-	-	++	-	++	-	-
Executive deficits	+	+	+	-	+	-	+	-	-	+	±	-	+
Episodic memory deficits	-	+	-	+	-	-	-	-	+	-	+	+	-
Impaired confrontation naming	+	++	±	+	+	++	+	++	+	-	+	+	+
Impaired language comprehension	+	+	+	-	±	++	+	-	-	-	+	±	-
Prosopagnosia	+	+	-	-	+	+	+	-	+	-	-	+	+
Family history[b]													
Goldman score	1	3	1	3	3	2	4	5	5	4	4	2	3
Psychiatric Family history	-	-	-	-	+	+	-	-	+	-	-	-	+
Neuroimaging													
Temporal atrophy at first scan	R>L (3)	R>L (5)	L>R (2)	L>R (5)	S (6)[c]	S (6)	S (8)	R>L (8)	R>L (4)	S (6)	R>L(5)	S (5)[c]	S (10)
Temporal atrophy at follow-up		S (7)		S (6)				R>L (11)					

Supplementary Table 1. Clinical characteristics of 13 FTD patients carrying I383V *TARDBP* variant.

Patients are numbered according to their ID in the pedigrees (Figure 1 / Supplementary Figure 1). Four out of 13 patients have died (disease duration marked with asterisk), whereas current disease duration is presented for the nine living patients. *Clinical diagnoses:* bvFTD = behavioral variant of FTD; svPPA = semantic variant of primary progressive aphasia. *Clinical symptoms*: - = absent; ± = mild; + = moderate; ++ = severe. *Neuroimaging*: R = right; L = left; S = symmetric. The numbers in brackets indicate the number of years after symptom onset when neuroimaging was performed.

[a] Neuropathologic examination.

[b] Goldman score based on family history (up till 2nd degree).

[c] Computed tomography (CT) was performed instead of Magnetic Resonance Imaging (MRI).

	1B	**3I**	**3J**	**5N**
Gender	M	F	F	M
Age at onset	39	53	59	62
Disease duration (years)	6*	6	9*	1*
Clinical diagnosis	ALS	PSMA	ALS	ALS
Clinical symptoms				
Onset	Spinal	Spinal	Spinal	Spinal
EMG affected regions (N)[a]	1	0[d]	2	3
Diagnostic delay (months)[b]	12	64	24	8
Cognitive impairment	-	-	-	-
Family history[c]				
Goldman score	1	5	5	5
Psychiatric Family history	-	-	-	-

Supplementary Table 2. Clinical characteristics of four ALS patients carrying I383V *TARDBP* variant.

Patients are numbered according to their ID in the pedigrees (Figure 1 / Supplementary Figure 1). Three patients have died (disease duration marked with asterisk), whereas current disease duration is presented for patient 3I. Neuroimaging was not performed in these patients. *Clinical diagnoses:* ALS = amyotrophic lateral sclerosis; PSMA = progressive spinal muscular atrophy.

[a] Number of regions with features consistent with ALS according to the revised El Escorial criteria.[1]

[b] The diagnostic delay is presented to indicate the relative slow progression in patients 3I and 3J.

[c] Goldman score based on family history (up till 2nd degree).

[d] Denervation and reinnervation changes were present, though not fulfilling El Escorial criteria.

Authors	Number of patients (families)	Age at onset	Clinical Diagnosis	Predominant atrophy distribution	Family history
Ramos et al., 2020[2]	4 (2)	ND	FTD	ND	Positive
Ramos et al., 2019[3]	3 (3)	60	bvFTD	Temporal (left>right)	Negative
		58	svPPA	Temporal (bilateral) + Frontal	Positive
		66	svPPA	Temporal (left>right) + Frontal	Positive
Gelpi et al., 2014[4]	1 (1)	60	svPPA	Temporal (left, bilateral at autopsy)	Dementia
Caroppo et al., 2016[5]	4 (3)	65	bvFTD-ALS	Temporal (bilateral) + Parietal (mild)	ALS
		63	bvFTD	Temporal (bilateral) + Frontal	bvFTD
		51	bvFTD	Temporal (right>left) + Frontal + Hippocampal	bvFTD
		51	svPPA	Temporal (left>right)	Negative
Cheng et al., 2016[6]	3 (1)	38	ALS	No atrophy	FTD, ALS
		64	svPPA	Temporal (left>right)	FTD, ALS
		62	bvFTD-ALS	Temporal (bilateral) + Frontal	FTD, ALS
Coyle-Gilchrist et al., 2016[7]	1 (1)	49	svPPA	Temporal (bilateral)	Unknown
Gonzalez-Sanchez et al., 2018[8]	2 (1)	51	svPPA	Temporal (left>right)	dementia, ALS
		52	ALS	ND	dementia, svPPA
Rutherford et al., 2008[9]	1 (1)	59	ALS	ND	ALS
Ticozzi et al., 2011[10]	3 (1)	66	ALS	ND	ALS
		25	ALS	ND	ALS
		57	ALS	ND	ALS
Ozoguz et al., 2015[11]	2 (1)	42	ALS	ND	ALS
		47	ALS	ND	ALS

Supplementary Table 3. Clinical characteristics of previously reported patients carrying the I383V *TARDBP* variant.

A total of 24 patients with the I383V variant from 17 different families have been reported in the literature. Eight of these patients were diagnosed with isolated ALS, whereas the majority was diagnosed with FTD or FTD-ALS. Neuroimaging of most FTD patients described the presence of temporal atrophy, in some cases combined with volume loss in other areas. *Clinical diagnoses:* ALS = amyotrophic lateral sclerosis; svPPA = semantic variant of primary progressive aphasia; bvFTD = behavioral variant of FTD. ND = not described.

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