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Frontotemporal lobar degeneration: genotype–phenotype links in TDP-43-associated disease

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Supplementary table 1 | **Included *TBK1* loss-of-function mutation carriers**

Publication	TBK1 mutation	Clinical diagnosis
Black et al.	p.A705fs	MND
	p.E476fs	MND
	p.R444X	MND
Borghero et al.	p.Met690fs	ALS
Caroppo et al.	p.Thr156ArgfsX6	1)FTD 2) ALS
	p.Thr156ArgfsX6	ALS
	p.Tyr482X	1)FTD 2) ALS
	p.Gln655X	1)FTD 2) ALS
	p.Leu654LysfsX18	1)FTD 2) ALS
Freischmidt et al.	p.Thr320GlnfsX40	ALS
	p.Thr320GlnfsX40	ALS
	p.Ile450LysfsX15	ALS
	p.Ile450LysfsX15	ALS-D
	p.Ile450LysfsX15	PBP
	p.Ile450LysfsX15	ALS
	p.Ile450LysfsX15	ALS
	p.Ile450LysfsX15	ALS
	p.Ile450LysfsX15	ALS
	p.Val479GlufsX4	ALS-FTD
	p.Val479GlufsX4	ALS-FTD
	p.Tyr185X	ALS
	p.Tyr185X	ALS
	p.Tyr185X	ALS
	p.Tyr185X	ALS
	p.Thr77TrpfsX4	ALS
	p.Thr77TrpfsX4	ALS
	p.Ala417X	ALS
	p.Ala417X	FTD
	p.Ala417X	ALS
	p.Ala417X	PBP
	p.Ala417X	ALS-FTD
	p.Ala417X	PBP
	p.690-713del	ALS
	p.690-713del	ALS
	p.690-713del	ALS-FTD
	p.690-713del	mono paresis
	p.690-713del	FTD
	p.690-713del	PBP
	p.690-713del	ALS-FTD
	p.690-713del	FTD
	p.690-713del	FTD
	p.Arg440X	ALS
	p.Arg440X	ALS-FTD
	p.Arg440X	ALS
	p.Arg440X	ALS
	p.Arg440X	FTD

	p.Glu643del	ALS
	p.Glu643del	ALS
Kim et al.	p.Ile472SerfsX8	ALS
Koriath et al.	p.Ala705fs	FTD
Pottier et al.	p.Arg117X	PPA
Pozzi et al.	p.Leu59PhefsX16	ALS
	c.358+5G>A	PLMND
Tohnai et al.	p.Arg357X	ALS
	p.Pro378_Ile379del	ALS
	p.Thr419_Gly420del	ALS
Tsai et al.	p.Arg444X	FTD-ALS
van der Zee et al. (# Schönecker et al.)	p.Gln*2	FTD
	p.Lys29ArgfsX15	FTD
	p.Val97PhefsX2	ALS
	p.Arg117X	FTD
	p.Arg127X	ALS
	p.Trp445X	FTD
	p.Ala417X	FTD
	p.Thr79del	FTD-ALS
	p.Thr462LysfsX3 #	ALS-FTD
	p.Thr462LysfsX3 #	ALS-D
Van Mossevelde et al.	p.Glu643del	ALS
	p.Glu643del	FTD
	p.Glu643del	D
	p.Glu643del	FTD
	p.Glu643del	FTD-ALS
	p.Glu643del	D
	p.Glu643del	FTD
	p.Glu643del	ALS
	p.Glu643del	ALS
	p.Glu643del	ALS
	p.Glu643del	FTD
	p.Glu643del	FTD
	p.Gly272_Thr331del	FTD
	p.Ser398ProfsX11	ALS
	p.Ser518LeufsX32	ALS
	p.Asp167del	ALS
Wilke et al.	p.Glu643del	PSPS
	p.Glu643del	ALS
	p.Glu643del	PCA
Williams et al.	p.Leu399fs	ALS

Font color black: index patients, font color grey: relatives. Abbreviations: ALS: amyotrophic lateral sclerosis; D: unspecified dementia; FTD: frontotemporal dementia; MND: motor neuron disease; PBP: progressive bulbar palsy; PCA: progressive cerebellar ataxia; PSPS: progressive supranuclear palsy syndrome; PLMND: pure lower motor neuron disease; PPA: primary progressive aphasia

Supplementary table 2 | **Reported phenotypic characteristics of *TBK1* mutation carriers**

Publication			**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**
Patients, n (index)			3 (3)	1 (1)	5 (4)	39 (15)	1 (1)	1 (1)	1 (1)	2 (2)	*2 (1)*[2]	1 (1)	3 (3)	*9 (9)*[2]	16 (10)	1 (1)	3 (2)
Diagnosis, n (index)	**(FT)D**		0	0	0	5[1] (0)	0	1 (1)	1 (1)	0	0	0	0	5 (5)	8 (4)	0	0
	MND		3 (3)	1 (1)	1 (0)	27 (13)	1 (1)	0	0	2(2)	0	0	3 (3)	2 (2)	7 (5)	1 (1)	1 (0)
	(FT)D-ALS		0	0	4 (4)	7 (2)	0	0	0	0	*2 (1)*[2]	1 (1)	0	*2 (2)*[2]	1 (1)	0	0
	PSPS		0	0	0	0	0	0	0	0	*0*	0	0	*0*	0	0	1 (1)
	PCA		0	0	0	0	0	0	0	0	*0*	0	0	*0*	0	0	1 (1)
Subdiagnosis, n (index)	**FTD variant**	**bvFTD**	NA	NA	0		NA	1 (1)	0	NA	*1 (1)*[2]	1 (1)	NA	*5 (5)*[2]	6 (4)	NA	NA
		PPA: nfv / sv	NA	NA	2 (2) / 2 (2)		NA	0	1 (1) / 0 (0)	NA	0	0	NA	1 (1) / 0	0 / 1 (1)	NA	NA
	ALS onset	**Bulbar**	2 (2)	0	0	4 (3)	1 (1)	NA	NA	0	0	0	2 (2)	2 (2)	4 (3)	0	
		Spinal	1 (1)	1 (1)	5 (4)	24 (11)	0	NA	NA	2 (2)	*1 (1)*[2]	1 (1)	1 (1)	*1 (1)*[2]	2 (1)	1 (1)	
Tot:behavioral feature, n (index)	**Apathy / reduced empathy**			0	3 (3)*		0	1 (1)	1 (1)		0	0			5 + 3* (2 + 2*)	0	2 (2)
	Disinhibition			0	2 (2)*		0	0	0		1 (0)*	1 (1)			6 + 1* (4 + 1*)	0	1 (1)
	Stereotype / compulsive			0	3 (3)*		0	1 (1)	1 (1)		0	0			6 (5)	0	0
Executive dysfunction, n (index)				0	1 (1)*		0	1 (1)*	1 (1)		0	0			4 (2)	0	
Memory / orientation difficulties, n (index)				0	0		0	1 (1)*	1 (1)		2 (1)	0	0		9 (5)	1 (1)*	1 (1)*
Language feature, n (index)	**Economy of speech / mutism**			0	0		0	0	1 (1)		0	0			4 (3)	0	0
	Semantic difficulties			0	2 (2)		0	1 (1)*	1 (1)		0	0			1 (1)	1 (1)*	0
	Agrammatic / non fluent			0	2 (2)		0	0	1 (1)		0	0		1 (1)[3]	0	1 (1)*	0
Psychiatric symptoms, n (index)				0	0		0	0	0		0	0			7 (2)	0	
Prosapognosia, n (index)				0	0		0	1 (1)*	0		0	0			1 (1)	0	
Apraxia, n (index)				0	1 (1)		0	0	0		0	0			2 (0)	0	0
Parkinsonism,	**Akinetic-rigid**			0	2 (2)		0	0	1 (1)		1 (0)	0			4 (2)	0	1 (1)

n (index)	**tremor-dominant**		0	0		0	0	0		0	0			1 (1)	0	0
Bulbar symptoms, n (index)	**In pure (FT)D**	NA	NA	NA	1 (0)	NA		1 (1)		NA	NA			2 (1)	NA	NA
	In spinal onset MND		1 (1)	2 (2)	17 (9)	NA	NA	NA		1 (1)	1 (1)			2 (1)	1 (1)	NA
Predominant UMN/LMN, n (index)					3 (1) / 1 (0)	1 (1) / 0 (0)	NA	0	0 / 1 (1)	0 / 1 (1)				6 (4) / 1 (1)	0 (0) / 1 (1)	0 (0) / 0 (0)
Atrophy on structural brain imaging, n (index)	**Present**			3 (3)			0	1 (1)		2 (1)				9 (5)	0	2 (2)
	Predominant frontotemporal cortical			3 (3)			0	1 (1)		2 (1)				5 (3)	NA	0 (0)
	Medial temporal/ hippocampi involved			1 (1)			0	0		0				3 (2)	NA	0 (0)
	Parietal lobes involved			0			0	0		0				1 (1)	NA	0 (0)
	Aspecific global			0			0	0		0				1 (0)	NA	0
	Mesencephalic			0			0	0		0				0	NA	2 (2)
	Cerebellar			0			0	0		0				0	NA	1 (1)
	Asymmetry no / yes			0 / 3 (3)			0	0 / 1 (1)						4 (2) / 5 (3)	NA	
Functional impairment, n (index)	**Present**			2 (2)			1 (1)	1 (1)		2 (1)	1 (1)			3 (3)		
	Predominant frontal and/or temporal			2 (2)			1 (1)	1 (1)		1 (0)	1 (1)			3 (3)		
	Medial temporal/ hippocampi involved			1 (1)			1 (1)	0		1 (1)	0			0		
	Subcortical involvement			0			1 (1)	0		1 (1)	0			0		
	Parietal lobes involved			0			1 (1)	0		2 (1)	0			3 (3)		
	Asymmetry no / yes			0 / 2 (2)			0 / 1 (1)	0 / 1 (1)		1 (1) / 1 (0)				0 / 3 (3)		

no information available; * later in disease course; [1]one relative initially diagnosed as AD; [2]index patient of Schönecker et al. is also included in van der Zee et al., is adjusted in the total number of table 1 in main paper; [3]derived from PNFA diagnosis in one patient. ***Abbreviations:*** ALS: amyotrophic lateral sclerosis; D: unspecified dementia; FTD: frontotemporal dementia; ; (FT)D: frontotemporal dementia or unspecified dementia; MND: motor neuron disease; NA: not applicable; nfv: non fluent variant; PCA: progressive cerebellar ataxia; PPA: primary progressive aphasia; PSPS: progressive supranuclear palsy syndrome; sv: semantic variant; A: Black et al. 2017; B: Borghero et al. 2015; C: Caroppo et al. 2015; D: Freischmidt et al. 2015; E: Kim et al. 2017; F: Koriath et al. 2017; G: Pottier et al. 2015; H: Pozzi et al. 2017; I: Schönecker et al. 2016; J: Tsai et al. 2016; K: Tohnai et al. 2017 L: van der Zee et al. 2017; M: Van Mossevelde et al. 2016; N: Williams et al. 2015; O: Wilke et al. 2017

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