1874-2203/20

Open Medicine Journal

Content list available at: https://openmedicinejournal.com

Supplementary Material

Early-onset of Frontotemporal Dementia and Amyotrophic Lateral Sclerosis in an Albanian Patient with a c.1319C>T Variant in the *UBQLN2* Gene

Mirko Baglivo[1], Elena Manara[1,*], Natale Capodicasa[2], Paolo Enrico Maltese[3], Liborio Stuppia[4], Sandro Michelini[5], Rita Compagna[6], Bruno Amato[6] and Matteo Bertelli[1]

[1]*Magi Euregio, Bolzano, Italy*
[2]*Magi Balkans, Tirana, Albania*
[3]*Magi's lab, Rovereto, Trento, Italy*
[4]*Department of Psychological, Health and Territorial Sciences, School of Medicine and Health Sciences, "G. d'Annunzio" University, Chieti-Pescara, Italy*
[5]*Department of Vascular Rehabilitation, San Giovanni Battista Hospital ACISMOM, Rome, Italy*
[6]*Department of Public Health, University of Naples Federico II, Naples, Italy*

Abstract:

Background:

Frontotemporal Dementia (FTD) is the second most common cause of dementia under 65 years of age; it has a prevalence of 4-15 per 100,000 persons. The overt disease usually manifests in the sixth decade, and it is extremely rare to find affected patients in their twenties.

Objective:

Here, we present the clinical and molecular genetic findings of an Albanian family with a patient with early-onset FTD and Amyotrophic Lateral Sclerosis (ALS).

Methods:

Given the great variability of clinical presentation of FTD and the number of genes involved, targeted Next Generation Sequencing (NGS) was used to screen the DNA of the 27-year-old male patient. Segregation analysis was performed in available family members.

Results:

A variant, consisting of a proline-leucine amino acid substitution in position 440, was identified in the *UBQLN2* gene on the X-chromosome. This variant was previously reported as a variant of unknown significance in a 30-year-old female patient with amyotrophic lateral sclerosis. With the description of our case, we add evidence on its involvement, also in ALS-FTD. The variant is in a functional domain important for interaction with HSP70 and this, in turn, may impair the shuttling of proteins to the proteasome leading to an accumulation of protein aggregates. The variant was inherited from the unaffected mother, in line with the fact that incomplete penetrance has been widely described for this gene.

Conclusion:

The present report adds information regarding one of 34 variants in the *UBQLN2* gene reported so far in association with neurodegeneration and proposes a molecular pathogenesis of ALS-FTD in this patient.

Keywords: Frontotemporal dementia, Ubiquilin2 gene, *UBQLN2*, Amyotrophic lateral sclerosis, X-linked, HSP70.

Article History	Received: April 22, 2020	Revised: June 23, 2020	Accepted: July 01, 2020

Table S1. List of genes tested by NGS. Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; PD, Parkinson's disease; EOD, early onset dementia.

GENE	CHROMOSOME	NCBI Ref. Seq.	OMIM	DISEASE
APOE	chr19	NM_000041	107741	AD
APP	chr21	NM_000484	104760	AD

(Table S1) cont.....

GENE	CHROMOSOME	NCBI Ref. Seq.	OMIM	DISEASE
C9orf72	chr9	NM_001256054	614260	ASL/FTD
CHMP2B	chr3	NM_014043	609512	FTD
CSF1R	chr5	NM_005211	164770	
DCTN1	chr2	NM_004082	601143	PD/ALS/FTD
FUS	chr16	NM_004960	137070	ALS/FTD
GRN	chr17	NM_002087	138945	FTD
ITM2B	chr13	NM_021999	603904	dementia
MAPT	chr17	NM_005910	157140	FTD
PRNP	chr20	NM_000311	176640	
PSEN1	chr14	NM_000021	104311	AD
PSEN2	chr1	NM_000447	600759	AD
SIGMAR1	chr9	NM_005866	601978	ALS
SORL1	chr11	NM_003105	602005	
SQSTM1	chr5	NM_003900	601530	ALS/FTD
TARDBP	chr1	NM_007375	605078	ALS/FTD
TBK1	chr12	NM_013254	604834	ALS/FTD
TREM2	chr6	NM_018965	605086	EOD
UBE3A	chr15	NM_130838	601623	
UBQLN2	chrX	NM_013444	300264	ALS/FTD
VCP	chr9	NM_007126	601023	ALS/FTD

Table S2. List of 34 UBQLN2 variants identified and reported in the literature and in HGMD (http://www.hgmd.cf.ac.uk).

UBQLN2 Domain	Nucleotide variant (NM_013444)	Amino acid variant (NP_038472)	HGMD Variant class	Note	References	Age of onset	Sex	Symptoms	Family screening	Familial/ sporadic	Incomplete penetrance	Reported phenotype
ubl-sti1	**c.252A>T**	p.Q84H	DM?	Found another variant	(Tripolszki *et al*., 2019)	-	N/A	ALS	-	N/A	-	Amyotrophic lateral sclerosis
	c.401C>T	p.T134I	DM	-	(Bartoletti-Stella *et al*., 2018)	N/A	N/A	Probable AD dementia with high evidence of AD pathophysiological process	-	familial	-	Alzheimer's disease
	c.464G>A	p.S155N	DM	-	(Daoud *et al*., 2012)	N/A	M	ALS without signs of dementia	-	sporadic	-	Amyotrophic lateral sclerosis
STI1-1	**c.565C>A**	p.P189T	DM	-	(Daoud *et al*., 2012)	N/A	F	ALS without signs of dementia	-	sporadic	-	Amyotrophic lateral sclerosis

(Table S2) cont.....

UBQLN2 Domain	Nucleotide variant (NM_013444)	Amino acid variant (NP_038472)	HGMD Variant class	Note	References	Age of onset	Sex	Symptoms	Family screening	Familial/	Incomplete penetrance	Reported phenotype
STI1-2/ STI1-3	**c.845C>T**	p.A282V	DM	-	(Synofzik *et al*., 2012)	54	M	progressive apathy, emotional blunting, loss of insight in everyday life difficulties, and disease symptoms, restless wandering, and concentration deficits.	-	mother with variant, but healthy	yes	Frontotemporal Dementia
	c.847G>A	p.A283T	DM	-	(Synofzik *et al*., 2012)	72	M	ALS: distal atrophy and flaccid paresis of the right lower extremity, followed by mild spasticity in both legs	-	sporadic	-	Amyotrophic lateral sclerosis
	c.942T>A	p.D314E	DM?		(Kim *et al*., 2014)				5 healthy carriers	sporadic		- Amyotrophic lateral sclerosis
	c.1001C>T	p.T334M	DM?	C9orf72 expansion	(Morgan *et al*., 2017)	-	-	-	-	-	-	Amyotrophic lateral sclerosis
	c.1006A>G	p.T336A	DM?	-	(Lattante *et al*., 2013)	N/A	M	-	1 healthy carrier	familial	yes	Frontotemporal lobar degeneration
	c.1019G>T	p.S340I	DM		(Kotan *et al*., 2016)rs	63	F	Frequent falls, speech disorders, amnesia, changes in mood and temperament	same symptoms in four sisters and one niece around age 50 years	familial	-	Amyotrophic lateral sclerosis
					(Özoğuz *et al*., 2015)	20	M			familial	yes	
						40	F					
						12	M					
					(Dillen *et al*., 2013)	62	F	-	-	-	yes	
	c.1037C>G	p.S346C	DM?	-	(Dillen *et al*., 2013)	77	F	FTD	no segregation analysis performed	sporadic	-	Frontotemporal lobe degeneration
STI1-3	**c.1176G>A**	p.M392I	DM		(Özoğuz *et al*., 2015)	16	M	ALS: Drop foot	-	sporadic	-	Amyotrophic lateral sclerosis
						14	F	ALS: Madras-type MND	-	sporadic	-	
	c.1174A>G	p.M392V	DM?	-	(Huang *et al*., 2017)	62	M	ALS with progressive upper limb weakness	no segregation analysis performed	sporadic	-	Amyotrophic lateral sclerosis
	c.1198A>G	p.S400G	DM?	-	(Dillen *et al*., 2013)	78	F	ALS	Variant also present in healthy family members	Sporadic	-	Amyotrophic lateral sclerosis
	c.1274A>G	p.Q425R	DM	-	(Synofzik *et al*., 2012)	51	F	ALS; slowly progressive bilateral distal atrophy of hand muscles, followed by bilateral atrophy also of the distal leg muscles within the next 10 years	1 aunt with late-onset dementia	familial	-	Amyotrophic lateral sclerosis
STI1-4	**c.1316A>T**	p.N439I	DM?	-	(Gellera *et al*., 2013)	-	F	-	found in one control subject	-	-	-
	c.1319C>T	p.P440L	DM/DM?	-	(Dillen *et al*., 2013)	30	F	ALS	-	familial	Yes	Amyotrophic lateral sclerosis
					This report	24	M	FTD	-	familial	yes	Frontotemporal Dementia
	c.1337T>G	p.M446R	DM?	found with pathogenic variant in TARDBP	(Gellera *et al*., 2013)	43	F	ALS with spinal onset	mother affected	familial	-	Amyotrophic lateral sclerosis
	c.1379A>G	p.Q460R	DM?	Found with pathogenic variant in SOD1	Morgan (2017) Brain	-	-	-	-	-	-	-

(Table S2) cont.....

UBQLN2 Domain	Nucleotide variant (NM_013444)	Amino acid variant (NP_038472)	HGMD Variant class	Note	References	Age of onset	Sex	Symptoms	Family screening	Familial/	Incomplete penetrance	Reported phenotype
STI1-4 /pxx	**c.1400C>T**	p.T467I	DM?	-	(Ugwu *et al*., 2015)	70	F	FTD	-	familial	-	Frontotemporal lobar degeneration
	c.1460C>T	p.T487I	DM		(Williams *et al*., 2012)	35	F	ALS	11 family members affected with ALS	familial	-	Amyotrophic lateral sclerosis
						34	M	ALS	11 family members affected with ALS	familial	-	Amyotrophic lateral sclerosis
	c.1462G>A	p.A488T	DM	-	(Teyssou *et al*., 2017)	47	M	ALS, with progressive proximal weakness of lower limbs	-	sporadic	-	Amyotrophic lateral sclerosis
PXX	**c.1481C>T**	p.P494L	DM	-	(Teyssou *et al*., 2017)	55	F	ALS onset at upper limbs	father 72-years affected and died for FTD-ALS, sister with variant but healthy	familial	incomplete penetrance	Amyotrophic lateral sclerosis
	c.1489C>T	p.P497S	DM		(Deng *et al*., 2011)	25	F	ALS	8 affected family members	-	yes	Amyotrophic lateral sclerosis
						29	M	ALS/dementia	9 affected family members	-	yes	Amyotrophic lateral sclerosis
	c.1490C>A	p.P497H	DM	-	(Deng *et al*., 2011)	37	F	ALS	19 family member affected	familial	-	Amyotrophic lateral sclerosis
					(Deng *et al*., 2011)	19	M	ALS	19 family member affected	familial	-	
					(Gellera *et al*., 2013)	33	M	FTD signs, bulbar ALS at age 33 years	affected mother	familial	-	
					(Gkazi *et al*., 2019)	39	M	ALS, spastic paraplegia, and FTD	5 other family members with symptoms of ALS	familial	-	
	c.1490C>T	p.P497L	DM		(Fahed *et al*., 2014)	25	F	progressive choreoathetoid movements, dysarthria, dysphagia, spastic paralysis, and behavioral dementia	other 6 family members with symptoms	familial	-	Neurodegeneration, X-linked
						4	M	progressive choreoathetoid movements, dysarthria, dysphagia, spastic paralysis, and behavioral dementia	other 6 family members with symptoms	familial	-	Neurodegeneration, X-linked
	c.1498C>T	p.P500S	DM	-	(Teyssou *et al*., 2017)	60	F	ALS of upper limbs	mother with ALS and bulbar involvement since age 75 years	familial	full penetrance	Amyotrophic lateral sclerosis
	c.1516C>G	p.P506A	DM	-	(Teyssou *et al*., 2017)	45	M	Upper motor neurons involvement, SP diagnosis; Lower motor neuron involvement and ALS diagnosis	Brother and grandparent with SP; uncle with ALS	familial	yes	Amyotrophic lateral sclerosis

(Table S2) cont.....

UBQLN2 Domain	Nucleotide variant (NM_013444)	Amino acid variant (NP_038472)	HGMD Variant class	Note	References	Age of onset	Sex	Symptoms	Family screening	Familial/	Incomplete penetrance	Reported phenotype
PXX	**c.1516C>T**	p.P506S	DM	-	(Gellera *et al*., 2013)	30	M	ALS	mother's brother affected with ALS, spinal onset	familial	-	Amyotrophic lateral sclerosis
					(Özoğuz *et al*., 2015)	26	M	ALS	-	familial	-	
					(Vengoechea *et al*., 2013)	35	F	Femalehad ALS/FTD	-	familial	-	
					(Vengoechea *et al*., 2013)	32	M	brother, with ALS	-	familial	-	
					(Gkazi *et al*., 2019)	54	M	amyotrophic lateral sclerosis, spastic paraplegia, and frontotemporal dementia	2 other family membersaffected	familial	-	
	c.1516C>A	p.P506T	DM	-	(Deng *et al*., 2011)	40	F	ALS	-	familial	yes	Amyotrophic lateral sclerosis
						16	M	dementia	-	familial	-	-
	c.1525C>T	p.P509S	DM	-	(Deng *et al*., 2011)	53	F	ALS	2 affected sisters	familial	-	Amyotrophic lateral sclerosis
	c.1573C>T	p.P525S	DM		(Deng *et al*., 2011)	71	F	ALS	2 affected cousins, 2 healthy carriers	familial	yes	Amyotrophic lateral sclerosis
						70	M					
					(Özoğuz *et al*., 2015)	22	M	ALS	-	familial	yes	
					(Freudenberg-Hua *et al*., 2014)	-	-	-	-	-	-	
	c.1598C>T	p.P533L	DM?	Patient also had variant in OPTN	(Gellera *et al*., 2013)	33	F	ALS with spinal onset	affected mother	familial	-	Amyotrophic lateral sclerosis
	c.1612G>C	p.V538L	DM?	-	(Gellera *et al*., 2013)	57	F	Sporadic ALS with bulbar onset	no segregation performed	Sporadic	-	Amyotrophic lateral sclerosis