Supplementary Online Content

Le Ber I, Camuzat A, Guerreiro R, et al. *SQSTM1* mutations in French patients with frontotemporal dementia or frontotemporal dementia with amyotrophic lateral sclerosis. *JAMA Neurol*. Published online September 16, 2013.
doi:10.1001/jamaneurol.2013.3849.

eTable 1. List of the nonsynonymous, splice site variants and indels identified in family F297 by exome sequencing

eTable 2. In silico prediction of the functional impact of the *SQSTM1* missense mutations identified in this study

eTable 3. List of the rare missense variants identified in patients and French controls

eTable 4. List of the *SQSTM1* coding and noncoding variants identified in French patients and French controls

This supplementary material has been provided by the authors to give readers additional information about their work.

© 2013 American Medical Association. All rights reserved.

Downloaded From: http://archneur.jamanetwork.com/ by a University College London User on 10/13/2014

eTable 1. List of the nonsynonymous, splice site variants and indels identified in family F297 by exome sequencing

Genes	Chromosome	Exon	Amino acid change	SIFT*	PolyPhen2**	Mutation Taster***	Tissular expression	Protein
SQSTM1	5	7	p.P387L	Deleterious (score=0.00)	Possibly damaging (Score=0.870)	Disease causing (p-value=1.0)	ubiquitous/CNS	Sequestosome1/p62
CHD1L	1	13	p.P445S	Deleterious (score=0.00)	Possibly damaging (Score=1.000)	Disease causing (p-value=1.0)	ubiquitous/CNS	Chromodomain helicase DNA binding protein 1-like
PML	15	3	p.R382H	Deleterious (score=0.12)	Probably damaging (Score=1.000)	Polymorphism (p-value=0.999)	ubiquitous/CNS	Promyelocytic leukemia protein
SLCO3A1	15	10	p.T606M	Deleterious (score=0.02)	Probably damaging (Score=0.984)	Disease causing (p-value=1.0)	ubiquitous/CNS	Solute carrier organic anion transporter family, member 3A1
CDCA2	8	15	p.Q879E	Deleterious (score=0.02)	Possibly damaging (Score=0.884)	Polymorphism (p-value=0.986)	ubiquitous/CNS	Cell division cycle-associated protein 2
CACNA2D4	12	9	p.R352Q	Tolerated (score=0.14)	Probably damaging (Score=1.000)	Disease causing (p-value=0.7)	ubiquitous/CNS	Voltage-dependent calcium channel subunit alpha-2/delta-4
OTP	5	3	p.S253P	Deleterious (score=0.00)	Probably damaging (Score=0.995)	Disease causing (p-value=0.999)	ubiquitous/CNS	Orthopedia homeobox
IRGQ	19	3	p.W502G	Deleterious (score=0.00)	Possibly damaging (Score=0.518)	Polymorphism (p-value=0.563)	ubiquitous/CNS	Immunity-related GTPase family, Q
ZDHHC8	22	10	p.R637H	Deleterious (score=0.00)	Possibly damaging (Score=0.953)	Disease causing (p-value=1.0)	ubiquitous/CNS	zinc finger, DHHC-type containing 8
ZNF45	19	10	p.E329K	Deleterious (score=0.00)	Probably damaging (Score=1.000)	Disease causing (p-value=0.996)	ubiquitous/CNS	Zinc finger protein 45
PKP3	11	5	p.R413W	Deleterious (score=0.03)	Probably damaging	Disease causing (p-value=0.977)	ubiquitous/CNS	Plakophilin-3

© 2013 American Medical Association. All rights reserved.

Downloaded From: http://archneur.jamanetwork.com/ by a University College London User on 10/13/2014

					(Score=1.000)			
HDAC7	12	23	p.A877S	Deleterious (score=0.03)	Possibly damaging (Score=0.517)	Disease causing (p-value=1.0)	ubiquitous/CNS	Histone deacetylase 7
MYO7B	2	36	p.R1638C	Deleterious (score=0.03)	Probably damaging (Score=0.997)	Polymorphism (p-value: 1.0)	ubiquitous/CNS	Myosin VIIB
KLB	4	4	p.L776F	Deleterious (score=0.04)	Possibly damaging (Score=0.954)	Polymorphism (p-value=0.999)	ubiquitous/CNS	Klotho beta-like protein
SLCO1A2	12	7	p.A187T	Tolerated (score=0.34)	Possibly damaging (Score=0.909)	Disease causing (p-value=0.799)	ubiquitous/CNS	Solute carrier organic anion transporter family, member 1A2
TTC37	5	42	p.R1502W	Deleterious (score: 0.00)	Probably damaging (Score=1.000)	Disease causing (p-value=1.0)	ubiquitous/CNS	tetratricopeptide repeat domain 37
NEIL1	12	2	insGGCC, p.F23fsX	-	-	-	ubiquitous/CNS	Nei-Endonuclease VIII-Like 1

CNS: central nervous system. *SIFT: Scores less than 0.05 are predicted to be deleterious, **PolyPhen2: scores are evaluated as 0.000 (most probably benign) to 1.000 (most probably damaging), *** MutationTaster: a p-value close to 1 indicates a high 'security' of the prediction.

© 2013 American Medical Association. All rights reserved.

Downloaded From: http://archneur.jamanetwork.com/ by a University College London User on 10/13/2014

eTable 2. In silico prediction of the functional impact of the *SQSTM1* missense mutations identified in this study

Mutation	Exon	SIFT*	PolyPhen2**	MutationTaster***
p.A33V	1	Tolerated (score=0.08)	Benign (Score=0.008)	Polymorphism (p-value=1.0)
p.A381V	7	Tolerated (score=0.12)	Possibly damaging (Score=0.657)	Disease causing (p-value=1.0)
p.P387L	7	Deleterious (score=0.00)	Probably damaging (Score=0.870)	Disease causing (p-value=1.0)
p.P392L	8	Tolerated (score=0.22)	Probably damaging (Score=0.988)	Disease causing (p-value=1.0)

*SIFT: Scores less than 0.05 are predicted to be deleterious, **Polyphen2: PolyPhen-2: scores are evaluated as 0.000 (most probably benign) to 1.000 (most probably damaging), *** MutationTaster: a p-value close to 1 indicates a high 'security' of the prediction.

© 2013 American Medical Association. All rights reserved.

Downloaded From: http://archneur.jamanetwork.com/ by a University College London User on 10/13/2014

eTable 3. List of the rare missense variants identified in patients and French controls

rs number	cDNA	Exon	Amino acid change	Number of patients Heterozygous/ homozygous	Number of controls Heterozygous/ homozygous	SIFT*	PolyPhen2**	MutationTaster***
Synonymous changes								
-	c.183C>T	1	p.G61G	-	3 / 0	-	-	-
rs145037913	c.456C>T	3	p.S152S	-	1 / 0	-	-	-
-	c.771C>T	6	p.I257I	-	1 / 0	-	-	-
rs56092424	c.954C>T	6	p.S318S	4 / 0	15 / 1	-	-	-
rs143977783	c.1278G>A	8	p.A426A	-	1 / 0	-	-	-
Nonsynonymous changes								
rs139372286	c.328C>T	3	p.R110C	1 / 0	-	Deleterious (0.01)	Probably damaging (0.995)	Disease causing (p-value: 0.99)
rs11548633	c.712A>G	5	p.K238E	1 / 0	2 / 0	Tolerated (score: 0.35)	Possibly damaging (0.717)	Disease causing (p-value:1.0)
rs55793208	c.822G>C	6	p.E274D	8 / 1	13 / 1	Tolerated (score: 0.64)	Benign (0.000)	Polymorphism (p-value: 1.0)
rs200445838	c.833C>T	6	p.T278I	-	1 / 0	Tolerated (score: 0.07)	Benign (0.013)	Polymorphism (p-value: 1.0)
rs149743469	c.1029A>G	6	p.R312G	6 / 0	-	Tolerated (score: 0.40)	Benign (0.000)	Polymorphism (p-value: 1.0)
-	c.962G>A	6	p.R321H	1 / 0	-	Tolerated (score: 0.12)	Benign (0.007)	Polymorphism (p-value: 1.0)

*SIFT: Scores less than 0.05 are predicted to be deleterious, **PolyPhen2: scores are evaluated as 0.000 (most probably benign) to 1.000 (most probably damaging), *** MutationTaster: a p-value close to 1 indicates a high 'security' of the prediction. -: absent.

© 2013 American Medical Association. All rights reserved.

Downloaded From: http://archneur.jamanetwork.com/ by a University College London User on 10/13/2014

eTable 4. List of the *SQSTM1* coding and noncoding variants identified in French patients and French controls

rs number	cDNA* / protein**	Exonic / Intronic	Variants	Genotype & allele frequencies in French Patients (N=188)	Genotypes & allele frequencies in French controls (N=352)	Minor allele frequencies (MAF) in 1000genome database
rs189132632	c.-35G	5'UTR	G/G	0.100	0.997	
			G/C	0.000	0.003	
			C/C	0.000	0.000	
			G allele	1.00	1.00	
			C allele	0.00	0.00	C=0.014
rs74523483	c.-25G	5'UTR	G/G	0.100	0.997	
			G/A	0.000	0.003	
			A/A	0.000	0.000	
			G allele	1.00	1.00	
			A allele	0.00	0.00	A=0.013
rs200396166	c.98C>T / p.A33V	Exon 1	CC	0.995	0.100	
			C/T	0.005	0.000	
			T/T	0.000	0.000	
			C allele	1.00	1.00	
			T allele	0.00	0.00	NA
-	c.183C>T / p.G61G	Exon 1	C/C	0.100	0.992	
			C/T	0.000	0.008	
			T/T	0.000	0.000	
			C allele	1.00	1.00	
			T allele	0.00	0.00	NA
rs114761223	c.302-58C>T	Intron 2	C/C	1.000	0.994	
			C/T	0.000	0.006	
			T/T	0.000	0.000	
			C allele	1.00	1.00	
			T allele	0.00	0.00	T=0.015
rs139372286	c.328C>T / p.R110C	Exon 3	CC	0.995	1.000	
			C/T	0.005	0.000	
			T/T	0.000	0.000	
			C allele	0.99	1.00	
			T allele	0.01	0.00	NA

© 2013 American Medical Association. All rights reserved.

Downloaded From: http://archneur.jamanetwork.com/ by a University College London User on 10/13/2014

rs145037913	c.456C>T / p.S152S	Exon 3	C/C	1.000	0.997	
			C/T	0.000	0.003	
			T/T	0.000	0.000	
			C allele	1.00	1.00	
			T allele	0.00	0.00	NA
rs139142649	c.532-37C>T	Intron 3	C/C	1.000	0.997	
			C/T	0.000	0.003	
			T/T	0.000	0.000	
			C allele	1.00	1.00	
			T allele	0.00	0.00	T=0.001
rs115380981	c.532-23C>T	Intron 3	C/C	1.000	0.994	
			C/T	0.000	0.006	
			T/T	0.000	0.000	
			C allele	1.00	1.00	
			T allele	0.00	0.00	T=0.014
rs11948610	c.674-94G>A	Intron 4	G/G	0.994	1.000	
			G/A	0.006	0.000	
			A/A	0.000	0.000	
			G allele	1.00	1.00	
			A allele	0.00	0.00	A=0.037
rs11548633	c.712A>G / p.K238E	Exon 5	A/A	0.994	0.992	
			A/G	0.006	0.008	
			G/G	0.000	0.000	
			A allele	1.00	1.00	
			G allele	0.00	0.00	G=0.003
rs75363646	c.754+39C>A	Intron 5	C/C	0.988	0.960	
			A/C	0.002	0.036	
			A/A	0.000	0.004	
			C allele	0.99	0.98	
			A allele	0.01	0.02	A=0.009
rs2241349	c.755-23G>A	Intron 5	G/G	0.440	0.488	
			G/A	0.533	0.429	
			A/A	0.027	0.083	
			G allele	0.71	0.70	
			A allele	0.29	0.30	A=0.402

© 2013 American Medical Association. All rights reserved.

Downloaded From: http://archneur.jamanetwork.com/ by a University College London User on 10/13/2014

-	c.771C>T / p.I257I	Exon 6	C/C	1.000	0.997	
			C/T	0.000	0.003	
			T/T	0.000	0.000	
			C allele	1.00	1.00	
			T allele	0.00	0.00	NA
rs55793208	c.822G>C / p.E274D	Exon 6	G/G	0.951	0.957	
			G/C	0.044	0.040	
			C/C	0.005	0.033	
			G allele	0.97	0.98	
			C allele	0.03	0.02	C=0.009
rs200445838	c.833C>T / p.T278I	Exon 6	C/C	1.000	0.997	
			C/T	0.000	0.003	
			T/T	0.000	0.000	
			C allele	1.00	1.00	
			T allele	0.00	0.00	NA
rs4935	c.876C>T / p.D292D	Exon 6	C/C	0.209	0.288	
			C/T	0.692	0.500	
			T/T	0.099	0.212	
			C allele	0.55	0.54	
			T allele	0.45	0.46	C=0.316
rs149743469	c.934A>G / p.R312G	Exon 6	A/A	0.967	1.000	
			A/G	0.033	0.000	
			G/G	0.000	0.000	
			A allele	0.98	1.00	
			G allele	0.02	0.00	NA
rs4797	c.936G>A / p.R312R	Exon 6	G/G	0.203	0.265	
			G/A	0.670	0.470	
			A/A	0.126	0.265	
			G allele	0.52	0.50	
			A allele	0.48	0.50	G=0.419
rs56092424	c.954C>T / p.S318S	Exon 6	G/G	0.978	0.951	
			G/T	0.022	0.046	
			T/T	0.000	0.003	
			G allele	0.99	0.97	
			T allele	0.01	0.03	T=0.025

© 2013 American Medical Association. All rights reserved.

Downloaded From: http://archneur.jamanetwork.com/ by a University College London User on 10/13/2014

-	c.962G>A / p.R321H	Exon 6	G/G	0.995	1.000	
			G/A	0.005	0.000	
			A/A	0.000	0.000	
			G allele	0.99	1.00	
			A allele	0.01	0.00	NA
rs116830181	c.970-78C>T	Intron 6	C/C	1.000	0.987	
			C/T	0.000	0.013	
			T/T	0.000	0.000	
			C allele	1.00	0.99	
			T allele	0.00	0.01	T=0.043
rs155788	c.970-59T>C	Intron 6	T/T	0.821	0.818	
			T/C	0.179	0.166	
			C/C	0.000	0.016	
			T allele	0.91	0.90	
			C allele	0.09	0.10	C=0.186
-	c.1142C>T / p.A381V	Exon 7	C/C	0.994	1.000	
			C/T	0.006	0.000	
			T/T	0.000	0.000	
			C allele	1.00	1.00	
			T allele	0.00	0.00	NA
rs104893941	c.1175C>T / p.P392L	Exon 8	C/C	0.994	1.000	
			C/T	0.006	0.000	
			T/T	0.000	0.000	
			C allele	1.00	1.00	
			T allele	0.00	0.00	T=0.005
rs143977783	c.1278G>A / p.A426A	Exon 8	G/G	1.000	0.997	
			G/A	0.000	0.003	
			A/A	0.000	0.000	
			G allele	1.00	1.00	
			A allele	0.00	0.00	NA

*Accession number NM_003900.4; **Accession number NP_003891.1.

© 2013 American Medical Association. All rights reserved.

Downloaded From: http://archneur.jamanetwork.com/ by a University College London User on 10/13/2014