

Additional Table 1 Mitochondrial quality control processes that are altered by ALS causing genes

ALS-related gene	Gene function	Studied gene form	Study model	Mitochondrial quality control defects	Reference
SOD1	Anti-oxidative defense	G93A	Mice motor neurons	Activated mitophagy: degenerating mitochondria	Kong and Xu, 1998
		G93A	NSC-34 cells	Impaired MPQC: decreased Lon and Hsp70 expression	Fukada et al., 2004
		G93A	NSC-34 cells	Mitochondrial fragmentation	Raimondi et al., 2006
		G93A	Mice motor neurons	Impaired anterograde mitochondrial transport	De Vos et al., 2007
		G93A	Mice spinal cord, neuroblastoma cells	Increased Hsp70 expression	Yamashita et al., 2007
		G93A	NSC-34 cells	Mitochondrial fragmentation	Magrané et al., 2009
		G37R, G85R	Mice motor neurons	Mitochondrial fragmentation	Vande Velde et al., 2011
		G93A	Rat cortical and motor neurons	-Mitochondrial fragmentation only in motor neurons -Impaired mitochondrial transport only in motor neurons	Magrané et al., 2012
		G93A	Mice spinal cord and muscles	Impaired mitochondrial biogenesis: decreased expression of PGC-1 α and downstream factors	Thau et al., 2012
		G93A	Mice anterior half of lumbar spinal	Mitochondrial fragmentation: increased P-DRP1 and Fis1 levels versus decreased Mfn1 and OPA1 levels	Liu et al., 2013
		G93A	Mice skeletal muscles	-Impaired mitochondrial biogenesis: decreased PGC-1 α , PGC-1 β and NRF1 levels -Mitochondrial fragmentation: decreased Mfn1/2 levels	Russell et al., 2013
		G93A	Rat motor neurons	-Mitochondrial fragmentation -Impaired mitochondrial transport	Song et al., 2013
		G93A	Mice motor and sciatic nerves	-Mitochondrial fragmentation only in sciatic nerves -Impaired mitochondrial transport only in sciatic nerve	Magrané et al., 2014
		G93A	Mice motor neurons	Activated mitophagy: accumulation of mitochondria-containing autophagic vacuoles	Xie et al., 2015
		G93A	Mice brain stem, spinal cord and peripheral tissues	Impaired mitochondrial biogenesis: decreased PGC-1 α levels only in the nervous system	Bayer et al., 2017
TDP-43	RNA metabolism	WT, CTF	M17 human neuroblastoma cells	Mitophagy not activated: no conversion of LC3-I to LC3-II	Zhang et al., 2010
		WT, CTF	Fly photoreceptor neurons	Activated mitophagy: degenerating mitochondria and autophagic vacuoles only with WT TDP-43	Li et al., 2010
		WT	Mice brain neurons	Mitochondrial fragmentation: increased P-DRP1 and Fis1 levels versus decreased Mfn1 levels	Xu et al., 2010
		WT, M337V	Mice brain neurons	No mitochondrial fragmentation: Fis1 and Mfn1 levels unchanged	Xu et al., 2011
		WT, CTF, Q331K, M337V	NSC-34 cells	Activated mitophagy: increased LC3-II and decreased p62 on mitochondria	Hong et al., 2012
		WT, Q331K, M337V	Rat and mice motor neurons	-Mitochondrial fragmentation -Impaired mitochondrial transport	Wang et al., 2013
		WT, M337V	Mice brain neurons	Mitophagy not activated: no significant change in LC3 and p62 levels	Janssens et al., 2013
		A315T	Mice motor and sciatic nerves	-Mitochondrial fragmentation only in sciatic nerves -Impaired mitochondrial transport only in sciatic nerves	Magrané et al., 2014
		A315T	Mice brain neurons	-Impaired mitophagy: decreased Parkin levels -Mitochondrial fragmentation: decreased OPA1 levels	Stribl et al., 2014
		M337V	NSC-34 cells	Mitochondrial fragmentation	Finelli et al., 2015
		M337V	NSC-34 cells	Mitochondrial fragmentation	Finelli et al., 2015
		A382T	Patient fibroblasts	Mitochondrial fragmentation: increased Fis1 levels, Mfn1 levels unchanged	Onesto et al., 2016
A382T	Patient fibroblasts	Mitochondrial fragmentation: increased Fis1 levels, Mfn1 levels unchanged	Onesto et al., 2016		

Table 1 Continued

ALS-related gene	Gene function	Studied gene form	Study model	Mitochondrial quality control defects	Reference
		A382T	Patient fibroblasts	Mitochondrial fragmentation: increased Fis1 levels, Mfn1 levels unchanged	Onesto et al., 2016
		WT, M337V	Fly motor neurons	Unaltered mitochondrial transport	Baldwin et al., 2016
		WT, G298S, A382T	HEK293 cells, rat primary neurons, patient fibroblasts	Mitochondrial fragmentation	Wang et al., 2016
		WT, A315T	Mice motor cortex	Mitochondrial fragmentation	Wang et al., 2016
		WT, G298S	Fly brain neurons	Mitochondrial fragmentation: decreased Mfn levels	Khalil et al., 2017
FUS	RNA metabolism	WT, R521G, R521H	Mice motor neurons	Mitochondrial fragmentation only with FUS mutants	Tradewell et al., 2012
		WT, P525L	HT22 cells, mice and fly cortical neurons	Mitochondrial fragmentation	Deng et al., 2015
		WT, P525L	HEK293 cells	Activated mitophagy: increased PINK1, Parkin and Ub-Miro1 levels	Chen et al., 2016
		WT, P525L	Fly motor neurons	Impaired mitochondrial transport	Chen et al., 2016
C9orf72	Nucleocytoplasmic and endosomal trafficking, autophagy	GGGGCC mutant	Patient fibroblasts	-Mitochondrial fragmentation -Altered mitophagy: degenerating mitochondria and autophagic vacuoles, but LC3-I not converted to LC3-II -Impaired mitochondrial biogenesis: increased PGC-1 α levels	Onesto et al., 2016
VCP	Protein quality control, vesicle trafficking	A232E	MEFs	Reduced mitophagy	Kim et al., 2013
OPTN		E478G	HeLa cells	Reduced mitophagy: decreased LC3 recruitment to mitochondria	Wong and Holzbaur, 2014
	Autophagy, vesicle trafficking	E478G, Q398X	HeLa cells	Reduced mitophagy: decreased LC3 recruitment to mitochondria	Moore and Holzbaur, 2016
TBK1	Autophagy	E696K	HeLa cells	Reduced mitophagy: decreased LC3 recruitment to mitochondria	Moore and Holzbaur, 2016
CHCHD10	Mitochondrial cristae uncton and nucleoid regulation	S59L	Patient fibroblasts	Mitochondrial fragmentation	Bannwarth et al., 2014
VAPB	Vesicle trafficking, calcium signaling	WT, P56S	Rat cortical neurons	Reduced anterograde mitochondrial transport only with mutant VAPB	Morotz et al., 2012

ALS: Amyotrophic lateral sclerosis; CTF: C-terminal fragments; LC3: microtubule-associated protein 1A/1B-light chain 3; MEFs: murine embryonic fibroblasts; MPQC: mitochondrial protein quality control; P: phosphorylated; Ub, ubiquitinated; VAPB: vesicle-associated membrane protein-associated protein B/C; VCP: valosin-containing protein; WT: wild-type.