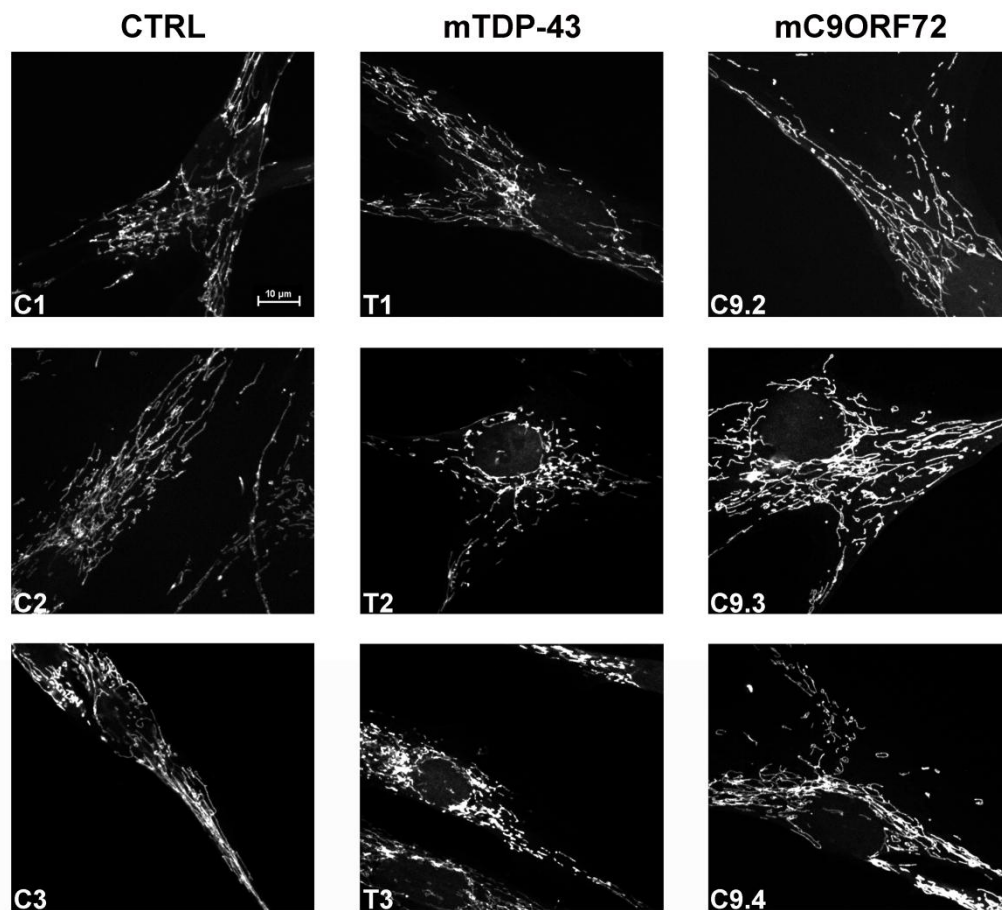
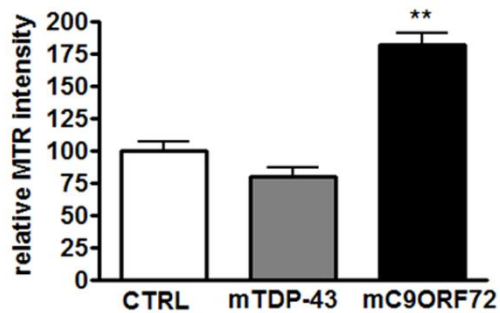


SUPPLEMENTARY DATA

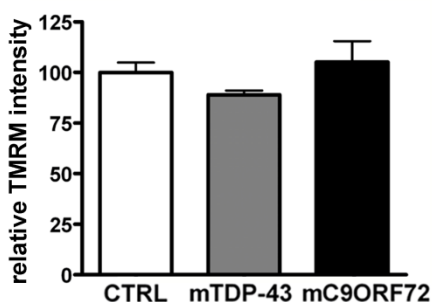
Supplementary Figure 1. Mitochondria morphology in mutant *TARDBP* and *C9ORF72* fibroblasts after 48 hours in galactose medium. Representative confocal images of mitochondrial network in primary fibroblasts from three healthy controls (C1, C2, C3), three ALS patients carrying mutation in *TARDBP* gene (p.A382T; T1, T2, T3) and three ALS/FTD patients with pathological expansion of the hexanucleotide repeat in *C9ORF72* (C9.2, C9.3, C9.4) transfected with pDsRed2Mito construct. Bar, 10 μ m.



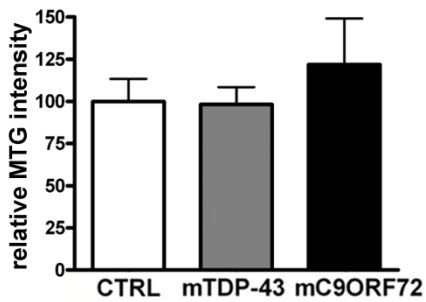
Supplementary Figure 2. Mitochondria functionality in mutant *TARDBP* and *C9ORF72* fibroblasts. Measurement of mitochondrial membrane potential by flow cytometry analysis of Mitotracker Red (MTR) positive fibroblasts (from 4 healthy controls, 3 *TARDBP* and 4 *C9ORF72* mutated patients) maintained in medium with galactose and without glucose. Median \pm SEM, n=3 different *DIV*; One-way ANOVA with Dunnett's multiple comparison test; **p<0.01).



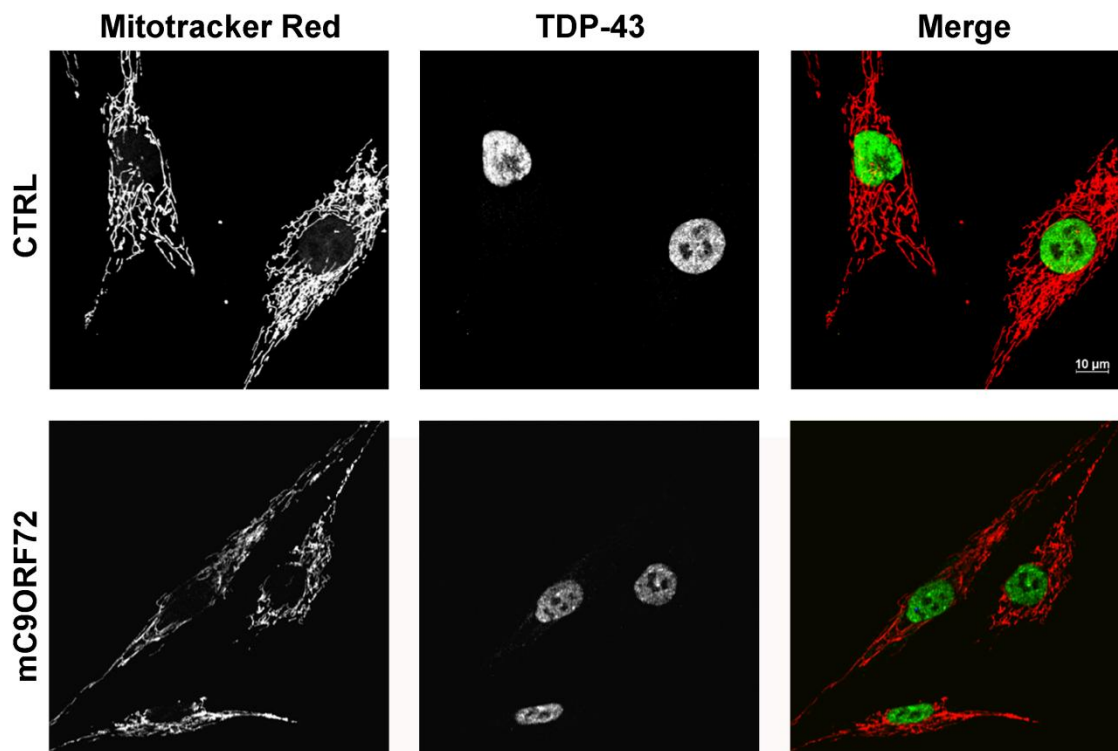
Supplementary Figure 3. Analysis of mitochondria membrane potential in mutant *TARDBP* and *C9ORF72* fibroblasts in glycolytic conditions. Measurement of mitochondrial (MMP) by flow cytometry analysis of TMRM-positive fibroblasts (4 healthy controls, 3 *TARDBP* and 4 *C9ORF72*), maintained in medium with 2 g/l glucose. Median \pm SEM, n=3 different *DIV*; One-way ANOVA with Dunnett's multiple comparison test).



Supplementary Figure 4. Analysis of mitochondria mass in mutant *TARDBP* and *C9ORF72* fibroblasts in glycolytic conditions. Measurement of mitochondrial mass (MM) by flow cytometry analysis of Mitotracker green (MTG)-positive fibroblasts (4 healthy controls, 3 *TARDBP* and 4 *C9ORF72*), maintained in medium with 2 g/l glucose. Median \pm SEM, n=3 different *DIV*; One-way ANOVA with Dunnett's multiple comparison test).



Supplementary Figure 5. TDP-43 sub-cellular localization in *C9ORF72* fibroblasts after 48 hours in galactose medium. Representative immunofluorescence images of TDP-43 (green) in primary fibroblasts from healthy controls (four) and ALS/FTD patients carrying mutation in *C9ORF72* gene (four), incubated with Mitotracker Red. Bar, 10 μ m.



Supplementary Table 1. Clinical features of healthy controls, *TARDBP*- and *C9ORF72*-mutated patients

Patient ID	Sex	Age at biopsy	Gene	Mutation	Diagnosis	Family history	Age at onset	Site of onset	Cognitive impairment
C1	M	37	-	-	-	-	-	-	-
C2	M	46	-	-	-	-	-	-	-
C3	F	53	-	-	-	-	-	-	-
C4	M	62	-	-	-	-	-	-	-
T1	M	26	<i>TARDBP</i>	p.A382T	ALS	No	25	spinal	No
T2	M	56	<i>TARDBP</i>	p.A382T	ALS	No	54	spinal	No
T3	F	60	<i>TARDBP</i>	p.A382T	ALS	No	59	spinal	No
C9-1	F	57	<i>C9ORF72</i>	1500 units	ALS	Yes (sister)	55	spinal	No
C9-2	M	64	<i>C9ORF72</i>	1166 units	ALS	No	61	spinal	No
C9-4	M	69	<i>C9ORF72</i>	>4000 units	ALS	No	66	spinal	No
C9-3	F	69	<i>C9ORF72</i>	2300 units	FTD	Yes (son with MND)	68	-	Yes

Supplementary Table 2. Primer sequences and probes for Quantitative Real time PCR

MAP1LC3 FOR	CAGCATCCAACCAAATCCC
MAP1LC3 REV	GTTGACATGGTCAGGTACAAG
P62 FOR	CCAGAGAGTTCCAGCACAGA
P62 REV	CCGACTCCATCTGTTCTCA
MT-ND5 FOR	GCAGCCATTCAAGCAATCCTA
MT-ND5 REV	AGGCGAGGATGAAACCGATAT
MT-ND5 MGB FAM probe	ACAACCGTATCGGCG

Supplementary Table 3. Respiratory electron transport chain activity. Values are expressed as nmol/min/mg protein and normalised with citrate synthase activity.

	Complex I	Complex II	Complex III	Complex IV	Succinate deidrogenase (SDH)
CTRL	36,9±4,9	11,7±1,2	66,0±4,9	108,9±12,5	9,7±0,2
mTDP-43.A382T	38,0±7,56	14,1±0,3	60,7±3,2	133,0±7,9	11,7±0,6
mC9ORF73	34,9±6,1	13,8±0,6	76,2±10,0	116,2±12,4	12,9±1,0