Supplementary table. Clinical, laboratory, radiology and genetical data of patients with TRMU associated disease. Patients 27 and 28 are P1 and P2 in the manuscript.

Patient	Sex	Age of onset	Age of death/last follow up	Liver failure	Neurological manifestations	Other clinical data	Blood lactate levels (mm/l)	Chain respiratory enzymatic activities	Histopathology	Brain MRI and other studies	**Genetics**	**Published by**
P1	ND	6m	2y	yes	no		Yes (5.5)	liver: CS normal, CI 29%, CII 66%, CII+III 43%, CIV 15%.// muscle: CS 21%, CI 71%, CII 95%, CII+III 76%, CIV 47%// mtDNA content ND.	3 MB normal. // 2 LB: minimal chronic inflammation and mild focal proliferation of bile ductus. Variable portal and sinusoidal fibrosis. Extensive oncotyc changes in the hepatocytes, focal macrovesicular steatosis and focal ballooning of cytoplasm.	EMG, NCV, echocardiogram, brain MRI, EEG, and ophthalmologic examinations: normal	homozygous c.232T>C, p.Tyr77His	[2]
P2	ND	4m	9m	yes	no		Yes (4.5)	liver: CS normal, CI 7%, CII 51%, CII+III 8%, CIV 22%.// mtDNA content 143%			homozygous c.232T>C, p.Tyr77His	[2]
P3	ND	2m	10y	yes	no		Yes (20)	liver: CS normal, CI ND, CII 75%, CII+III 34%, CIV 10%.// muscle: CS 38%, CI ND, CII 132%, CII+III 108%, CIV 82%// mtDNA content ND.			heterozygous c.232T>C, p.Tyr77His	[2]
P4	ND	3m	10y	yes	no	DCM, nephromegaly, proteinuria that resolved	Yes (6.6)	liver (6m after beginning acute phase, still symptomatic): CS 65%, CI ND, CII 260%, CII+III 141%, CIV 103%.// muscle: CS 64%, CI ND, CII 75%, CII+III 63%, CIV 60%// mtDNA content ND.		EMG, NCV, brain MRI, EEG, and ophthalmologic examinations: normal	homozygous c.232T>C, p.Tyr77His	[2]
P5	ND	4m	8y	yes	no		Yes (7)	ND		EMG, NCV, echocardiogram, brain MRI, EEG, and ophthalmologic examinations: normal	homozygous c.232T>C, p.Tyr77His	[2]
P6	ND	4m	14y	yes	no		Yes (20)	ND			homozygous c.232T>C, p.Tyr77His	[2]
P7	ND	3m	4m (D)	yes	no	MOF	Yes (30)	liver: CS normal, CI 11%, CII 65%, CII+III 12%, CIV16%.// mtDNA content 380%.			compound heterozygous c.232T>C, p.Tyr77His/c.706-1G>A	[2]
P8	ND	6m	2y	yes	no		Yes (3.2)	ND			compound heterozygous c.697C>T, p.Leu233Phe/ c.28G>T, p.Ala10Ser	[2]
P9	ND	1m	2m(D)	yes	no	death	Yes (19)	liver: CS normal, CI 25%, CII 70%, CII+III 17%, CIV ND.// mtDNA content 104%.			compound heterozygous c.835G>A, p.Val279Met /c.500-510del	[2]

P10	ND	6m	2y	yes	no		ND	liver: CS normal, CI 8%, CII 80%, CII+III 39%, CIV14%.// mtDNA content 104%.	LB (9m, still symptomatic): micronodule formation separated by delicate fibrous septae.cholestasis		homozygous c.815G>A, p.Gly272Asp	[2]
P11	ND	1d	5y	yes	no		Yes (20)	muscle: CS 75%, CI 42%, CII 97%, CII+III 89%, CIV29%.// mtDNA content 107%.			heterozygous c.40G>A, Gly14Ser	[2]
P12	ND	1d	3m(D)	yes	no	death	Yes (7)	muscle: CS ND, CI 12%, CII ND, CII+III 44%, CIV17%.// mtDNA content ND			homozygous c.2T>A, p.Met1Lys	[2]
P13	ND	2d	4m(D)	yes	no	death	Yes (10)	muscle: CS 68%, CI 14%, CII ND, CII+III 47%, CIV 22%.// mtDNA content 38%.			homozygous c.2T>A, p.Met1Lys	[2]
P14	F	4m	2y	yes	no		Yes (12.4)	Muscle: reduced C I and IV activities with normal C II/III and CS // liver: reduced C I to IV with normal CS. // Mitochondrial DNA deletions and mtDNA depletion were excluded	MB: slight fiber size variation and no ragged red fibers, increased lipid accumulation, NORMAL COX, SDH and combined reactions // LB: reticular fibrosis and incomplete cirrhosis with a micro nodular structure, swollen hepatocytes and increased fibrosis	normal MRI	compound heterozygous c.711_712insG / c.1081_1082insAG GCTGTGC	[5]
P15	F	3m	8m (D)	yes	axial and peripheral hypotonia		Yes (5); CSF (3.3)	Liver: Deficiencies of CI and CIV. The activity ratio of complex IV to complex I was strongly increased. Muscle: activities of all RC complexes were found markedly reduced (CV not performed). normal CS. Fibroblasts: activities of CIII CIV were decreased, normal activities of CII and CS.	LB: micronodular cirrhosis, an important canalicular cholestasis, and some oncotic change in hepatocytes. No steatosis.	myelination delay, normal MRS.	compound heterozygous c.835G>A, p.Val279Met /c.248+1G>A	[6]
P16	ND	4m	2y	yes	no	persistent multinodular liver	Yes (8-10), CSF (3.9)	Liver: Deficiencies of CI and CIV. The activity ratio of complex IV to complex I was strongly increased Fibroblasts: RC complexes normal	LB: portal and perisinusoidal fibrosis with microvesicular steatosis and oncocytic hepatocytes.	lactate peak on MRS	compound heterozygous c.835G>A, p.Val279Met /c.649G>A, p.Glu217Lys	[6]
P17	ND	2d	5y	yes	axial hypotonia, muscle weakness	persistent multinodular liver	Yes (4-6), CSF (2)	Liver: Deficiencies of CI and CIV. The activity ratio of complex IV to complex I was strongly increased	LB: signs of fibrosis, irregular cirrhosis with nodulation, severe cholestasis, and moderate macrovesicular steatosis. Some oncocytic and swollen hepatocytes were detected.	ND	homozygous c.697C>T, p.Leu233Phe	[6]

P18	M	birth	11y	no	ptosis, fatigability, bulbar involvement with feeding and respiratory difficulties		Yes (3.2), CSF (normal)	ND	MB (2m): variation in fibre size, increased lipids, reduced COs	ND	heterozygous c.28G>T, p.Ale10Ser	[7]
P19	F	6d	4y	yes	axial hypotonia, bulbar involvement,		Yes (7-18), CSF (2.4)	muscle: reduced CIV/ liver 2m: CIV reduced	MB (1m): variation in fiber size, increased lipid, reduced COX in oxidative staining and border // low COX in respiratory chain enzymes//hepatic biopsy: cell necrosis, balloon degeneration, microvesicular steatosis and cholestasis	abnormal unique high signal intensity in thalamus, (1m) reversible after 1ys, MRS lactate peak	compound heterozygous c.835G>A, p.Val279M and c.1102-3C>G	[7]
P20	M	birth	1m (D)	no	no	heart failure	ND	ND	ND	ND	homozygous c.287A>G, p.Asn96Ser	[8]
P21	ND	4m	ND	yes	microcephaly	Hypothyroidism, macrocytic anemia	Yes (ND)	ND	ND	ND	homozygous c.232T>C, p.Tyr77His	[9]
P22	ND	5m	ND	yes	microcephaly		Yes (ND)	ND	ND	ND	homozygous c.232T>C, p.Tyr77His	[9]
P23	F	4.5m	4.5y	yes	yes		Yes (ND)	liver: CS 436%, CI 126%, CII 220%, CIII 125%, CIV 63%.// muscle: normal	LB (3.5m): copper and copper-binding protein deposition in hepatocytes in a periportal distribution. portal tract fibrosis, cholangiopathy and small droplet steatosis. oncocytosis with microvesicular steatosis and normal mitochondrial morphology. // MB: done, but ND.	ND	compound heterozygous c.835G>A and c.1037-1040del TCAA	[10]
P24	M	3m	5y	yes	progressive irritability,	growth failure, ichthyosis.	Yes (ND)	muscle: CS 505%, CI 42.3%, CII 54.8%, CI+III 63.6%, CII+III 40%, CIV 17-6%	LB: ballooning degeneration, giant cell transformation, rosettes with cholestasis, apoptosis and necrosis. Absence of microvesicular steatosis // MB (4m): slight diffuse COX reduction with mild SDH increase in some fibers.	normal: echocardiogram, brain MRI, EEG, and ophthalmologic examinations	compound heterozygous: c.304A>c, p.Asn102Asp and c.835G>A; p.Val279Met	[11]

P25	F	4d	2m (D)	yes	seizure-like episodes	tachypnea, poor feeding.	Yes (14.8)	ND	ND	ND	compound heterozygous c.117G>A, p.W39X and c.680G>C, p.R227T	[12]
P26	M	2m	8m	yes	ND		Yes (41.9)	ND	ND	ND	compound heterozygous c.117G>A, p.W39X and c.680G>C, p.R227T	[12]
P27	F	3m	5m	yes	Generalized hypotonia, fluctuating level of consciousness, decreased intake, weight-loss		Yes (10)	MB: reduction of all complex activities and ratios, except CII. CS was increased (343 (153-304))	MB: Presence of few ragged red fibers. Variability in fiber size. Isolated fibers with increased SDH and NADH activity. Some fibers with diminished COX activity and COX positive granules.	MRI: T2W hyperintensity and restricted DWI of bilateral and symmetrical affectation of pontinus tracts, upper cerebellar peduncles, parahipocampal gyrus, dentate nuclei, globus pallidus and subcortical parietal white matter, and a lactate peak Abdominal ultrasound: increased size and echogenicity of the liver. EEG, Echocardiography, Ophthalmological assement: normal	Compound heterozygous: c.160_161delTG; p.Cys54* and c.680G>C; p.Arg227Thr	
P28	M	1d	25d	yes	Generalized hypotonia		Yes (>20)	MB: CS and complex activities except CII were low. The ratios between activities and CS were normal.	LB: massive microvesicular steatosis, showing few residual conserved hepatocytes.	MRI: symmetrical affectation of thalami, subthalamic nuclei and brainstem. MRS: lactate peak. Abdominal US: right grade I hydronephrosis, , including liver ultrasound. Ecocardiography and EKG: normal	c.2T>A; p.Met1? and c.491delT;p.Leu164ProfsTer22.	

Comentari [41]: Reviewer 1, comment 3

DCM dilated cardiomyopathy. EOM: extraocular movements. MB: muscle biopsy. LB: liver biopsy