



ARTICLE

Genotypic and phenotypic spectrum of infantile liver failure due to pathogenic *TRMU* variants

ARTICLE INFO

Article history:

Received 1 July 2022

Received in revised form

27 September 2022

Accepted 28 September 2022

Available online xxxx

Keywords:

Acute liver failure

Cysteine

Liver transplantation

Mitochondrial disease

Treatment

ABSTRACT

Purpose: The study aimed to define the genotypic and phenotypic spectrum of reversible acute liver failure (ALF) of infancy resulting from biallelic pathogenic *TRMU* variants and to determine the role of cysteine supplementation in its treatment.

Methods: Individuals with biallelic (likely) pathogenic variants in *TRMU* were studied through an international retrospective collection of de-identified patient data.

Results: In 62 individuals, including 30 previously unreported cases, we described 48 (likely) pathogenic *TRMU* variants, of which, 18 were novel. Of these 62 individuals, 42 were alive at a median age of 6.8 (0.6-22) years after a median follow up of 3.6 (0.1-22) years. The most frequent finding, occurring in all but 2 individuals, was liver involvement. ALF occurred only in the first year of life and was reported in 43 of 62 individuals, 11 of whom received liver transplantation. Loss-of-function *TRMU* variants were associated with poor survival. Supplementation with at least 1 cysteine source, typically N-acetylcysteine, improved survival significantly. Neurodevelopmental delay was observed in 11 individuals and persisted in 4 of the survivors, but we were unable to determine whether this was a primary or a secondary consequence of *TRMU* deficiency.

Conclusion: In most patients, *TRMU*-associated ALF is a transient, reversible disease and cysteine supplementation improved survival.

© 2022 The Authors. Published by Elsevier Inc. on behalf of American College of Medical Genetics and Genomics. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Introduction

The sudden onset of liver failure in an individual with no previous history of chronic hepatic dysfunction is termed acute liver failure (ALF). Knowledge of the underlying cause is key for decision-making about appropriate treatment, especially with regards to liver transplantation (LTX). Infections and inherited metabolic disorders are common causes of ALF and are typically confirmed using conventional diagnostic strategies for viral agents or metabolite screening. Increasingly, next-generation sequencing techniques have become the first-line diagnostic screening test and bridge the diagnostic gap in more than 30% of the cases

that remain unsolved after the application of conventional diagnostics.¹

TRMU is a nuclear gene encoding a crucial protein for mitochondrial translation, transfer RNA (tRNA) 5-methylaminomethyl-2-thiouridylate methyltransferase (*TRMU*), which catalyzes the important post-translation modification (thiolation) of mitochondrial tRNAs. Biallelic variants in *TRMU* underlie *TRMU* deficiency and were first described in association with infantile ALF.² In that original patient cohort of 13 individuals, 4 died of ALF, but the other 9 patients survived and showed no further hepatological or neurologic issues over the next 14 years of follow up. A further 23 cases have since been reported in the literature,³⁻¹⁶ with *TRMU*

Georg F. Vogel, Yael Mozer-Glassberg, and Yuval E. Landau contributed equally.

*Correspondence and requests for materials should be addressed to Georg F. Vogel, Department of Paediatrics I, Medical University of Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria. E-mail address: georg.vogel@i-med.ac.at

A full list of authors and affiliations appears at the end of the paper.

doi: <https://doi.org/10.1016/j.gim.2022.09.015>

1098-3600/© 2022 The Authors. Published by Elsevier Inc. on behalf of American College of Medical Genetics and Genomics. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

deficiency now termed as transient, infantile liver failure (OMIM 613070).

It is hypothesized that TRMU uses cysteine as the substrate for thiolation, and cysteine might be a conditionally essential amino acid in the first months of life.¹⁷ Therefore, L-cysteine or N-acetylcysteine (NAC) have been supplemented in individuals with TRMU deficiency, and anecdotal case reports showed beneficial effects.^{11,15} However, many individuals with TRMU deficiency are reported to require LTX.^{5,15}

TRMU deficiency is a disorder of the mitochondrial transcript processing and mitochondrial transfer RNA modification category (international classification of inherited metabolic disorder¹⁸). Consequently, the synthesis of mitochondrial DNA encoded proteins is impaired and mitochondrial respiratory chain function is severely compromised, resulting in disease. Many mitochondrial diseases are characterized by multiorgan involvement, including severe and progressive neurologic deterioration.

Hence, at least 4 important questions arise when a diagnosis of TRMU deficiency is made in an infant. What is the further course of disease? Is other organ involvement, especially neurologic involvement, to be expected? Will LTX be needed, and when should it be performed? Is supplementation with a cysteine source beneficial, and how long should this be continued?

In this article, we present a multicenter study of 62 patients with biallelic *TRMU* variants identified via international collaboration and literature review and seek to answer these questions in an evidence-based manner.

Materials and Methods

Study design and data acquisition

Individuals were included based on an international retrospective collection of de-identified data. Inclusion criteria were rare biallelic variants in *TRMU* classified as likely pathogenic or pathogenic according to the American College of Medical Genetics and Genomics/Association for Molecular Pathology guidelines.¹⁹ Eligible individuals were identified via literature review (eg, PubMed using the search term “TRMU”) and international collaborations. If individuals had been published previously, the respective authors were contacted for an update; if that was not received, only published data were included. All data were retrieved via standardized proformas agreed by participating centers.

For phenotyping, the following variables were analyzed within this study: individual’s genetic ancestry, sex, age at last assessment, and clinical status. In addition, detailed data on liver disease, laboratory values, and clinical features of the main organ systems involved were scrutinized and recorded according to Human Phenotype Ontology terminology.²⁰

Regarding standards of evidence for therapeutic studies, we used the grading system from the Centre for Evidence-

Based Medicine (<http://www.cebm.net>, ie, level 1c = all or none, which means [prolongation of] survival with therapy).

In silico modeling of *TRMU* missense variant pathogenicity scores

To assess the predicted effect of missense variants, commonly used prediction scores (mendelian clinically applicable pathogenicity v.3.5a and rare exome variant ensemble learner v.3.5a²¹⁻²³) were annotated for all biologically possible *TRMU* missense variants and mapped onto a linearized representation of the TRMU protein as previously shown.^{24,25} We generated all biologically possible base substitutions in the *TRMU* coding sequence (transcript: NM_018006.5) and used the Mutalyzer Position Converter to match the resulting variant call format file to the GRCh37/hg19 reference genome. Scores were annotated using the Ensembl variant effect prediction tool. A generalized additive model was built using the *geom_smooth* function of the R (R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. <https://www.R-project.org/>) ggplot 2 package to plot a smoothed line and CI.

Statistics and software

Kaplan-Meier estimates were calculated using R survival package. Bar and density plots were generated using the R ggplot2 package. Schematics and figures were compiled using Illustrator CS6 (Adobe).

Results

Study population

A total of 62 individuals (24 female, 9 sex not available [NA]) from 56 families residing in 18 countries were included, of whom, 32 were previously published²⁻¹⁶ (Tables 1 and 2). For 13 individuals, solely the published data were available (L-TRMU-49 to L-TRMU-62^{2,4,8,9,13,16}).

Of note, we did not include 1 previously published individual with compound heterozygosity for variants c.697C>T, p.(Leu233Phe) and c.28G>T, p.(Ala10Ser) (benign, found 1230 times in homozygous state in Genome Aggregation Database).² Data pertaining to respiratory chain enzyme activities, serum amino acid levels, organic acid profiles, and further laboratory findings are documented in Supplemental Table 1.

Genetics

A total of 48 different variants were identified, of these, 18 have not been reported previously (Table 1, Figure 1A). In 2

Table 1 Overview of *TRMU* variants of all individuals in this study

No.	Individual	Nucleotide Change NM_018006	Predicted Protein Change	Genomic Position: hg19_update	ACMG/AMP LoF Rating	Details of ACMG/AMP Rating	gnomAD Allele Frequency	Reference
1	TRMU-16	c.2T>C	p.?	46335766T>C	Yes	PTH	0	
2	L-TRMU-54, L-TRMU-55, L-TRMU-59	c.2T>A	p.?	46335766T>C	Yes	PTH	0	Zeharia et al, ² Sala-Coromina et al ¹⁶
3	L-TRMU-57	c.34_35dup	p.Gly13ProfsTer13	46335798-TC	Yes	LPTH	0	Qin et al ¹³
4	TRMU-15	c.37_48dup	p.Gly_Asp16dup	chr22-46335800 -CG...GA (12 bp)		LPTH	0.00003575	Murali et al ¹⁵
5	TRMU-8, TRMU-38	c.40G>A	p.Gly14Ser	46731701G>A		LPTH	6.47E-5	Zeharia et al ²
6	TRMU-7	c.44T>G	p.Val15Gly	46731705T>G		LPTH	0	
7	TRMU-30, TRMU-31	c.117G>A	p.Trp39Ter	46733710G>A	Yes	PTH	0	Soler-Alfonso et al, ¹¹ Murali et al ¹⁵
8	L-TRMU-58	c.162_163del	p.Cys54Ter	46337856-TG	Yes	PTH	0	Sala-Coromina et al ¹⁶
9	TRMU-19, TRMU-33, TRMU-34, TRMU-35, TRMU-36, TRMU-37, TRMU-47, TRMU-48, L-TRMU-49, L-TRMU-50, L-TRMU-51, L-TRMU-61, L-TRMU-62	c.229T>C	p.Tyr77His	46733822T>C		LPTH	0	Zeharia et al, ² Gil-Margolis et al ⁹
10	L-TRMU-57	c.244T>G	p.Phe82Val	46733837T>G		LPTH	0	Qin et al ¹³
11	TRMU-14	c.246C>G ^a	p.Phe82Leu	46337942C>G		LPTH	0	Murali et al ¹⁵
12	TRMU-5	c.248+1G>A	p.?	46337945G>A	Yes	PTH	0	Gaignard et al ⁵
13	TRMU-22, TRMU-23, TRMU-27, TRMU-46	c.287A>G	p.Asn96Ser	46739197A>G		LPTH	0	Taylor et al ⁶
14	L-TRMU-60	c.304A>G	p.Asn102Asp	46343317A>G		LPTH	0	Indolfi et al ⁸
15	TRMU-40	c.339T>G	p.Tyr113Ter	46739249T>G	Yes	PTH	0	
16	TRMU-42	c.383A>G	p.Tyr128Cys	46742346A>G		LPTH	0	Nicastro et al ¹⁰
17	L-TRMU-59	c.491del	p.Leu164ProfsTer22	46350303-T	Yes	LPTH	0	Sala-Coromina et al ¹⁶
18	TRMU-29	c.493C>A	p.Gln165Ter	46746202G>A	Yes	PTH	0	
19	L-TRMU-53	c.500_510del	p.Ala167GlufsTer36	46350312-CT...TT (11 bp)	Yes	PTH	0	Zeharia et al ²
20	TRMU-27	c.521C>T	p.Thr174Ile	46746230C>T		LPTH	0	
21	TRMU-14	c.525_527del	p.Phe176del	46350334-CTT		LPTH	0.00001193	Murali et al ¹⁵
22	TRMU-24	c.530T>A	p.Leu177His	46746239T>A		LPTH	0	
23	TRMU-44	c.581del	p.Gly194AspfsTer2	46746284-TG-T	Yes	PTH	0.00002475	
24	TRMU-1	c.589A>C	p.Lys197Gln	46746298A>C		LPTH	0	Kerr et al ¹²
25	TRMU-44	c.611C>T	p.Ala204Val	46746320C>T		LPTH	0	
26	TRMU-40	c.646_648del	p.Lys216del	46350458-AAA		LPTH	0	
27	TRMU-11	c.649G>A	p.Glu217Lys	46746358G>A		LPTH	0	Gaignard et al ⁵

(continued)

Table 1 Continued

No.	Individual	Nucleotide Change NM_018006	Predicted Protein Change	Genomic Position: hg19_update	LoF	ACMG/AMP Rating	Details of ACMG/AMP Rating	gnomAD Allele Frequency	Reference
28	TRMU-39, TRMU-41	c.653G>T	p.Ser218Ile	46748019G>T		LPTH	PM1, PM1, PM2, PP3, PP4, PP5	0	
29	TRMU-10	c.664T>G	p.Cys222Gly	46748030T>G		LPTH	PM1, PM2, PP3, PP4	0	
30	TRMU-45	c.671T>G	p.Ile224Ser	46748037T>C		LPTH	PM1, PM2, PP3, PP4, PP5	0	
31	TRMU-30, TRMU-31, L-TRMU-58	c.680G>C	p.Arg227Thr	46748046G>C		LPTH	PM1, PM2, PP3, PP4, PP5	0	Soler-Alfonso et al, ¹¹ Murali et al, ¹⁵ Sala-Coromina et al ¹⁶
32	TRMU-6	c.697C>T	p.Leu233Phe	46748063C>T		LPTH	PS3, PM1, PM2, PP4	0	Zeharia et al ²
33	TRMU-47, L-TRMU-49	c.706-1G>A	p?	46748160G>A	Yes	PTH	PVS1, PM2, PP5	0.000003976	Zeharia et al ²
34	TRMU-32	c.711dup	p.Gln238AlafsTer14	46748166_ 46748167insG	Yes	LPTH	PVS1, PM2	0	Schara et al ³
35	L-TRMU-52	c.815G>A	p.Gly272Asp	46353809G>A		LPTH	PP2, PM5, PM2	0	Zeharia et al ²
36	TRMU-20	c.827C>T	p.Pro276Leu	46749718C>T		LPTH	PM1, PM2, PP3, PP4	0	
37	TRMU-2, TRMU-3, TRMU-4, TRMU-5, TRMU-11, TRMU-17, TRMU-25, TRMU-26, TRMU-28, TRMU-42, TRMU-43, TRMU-45, L-TRMU-53, L-TRMU-56, L-TRMU-60	c.835G>A	p.Val279Met	46749726G>A		LPTH	PM1, PM2, PP3, PP4, PP5	0	Zeharia et al, ² Uusimaa et al, ⁴ Gaignard et al, ⁵ Grover et al, ⁷ Indolfi et al ⁸
38	TRMU-8	c.878C>T	p.Pro293Leu	46751345C>T		LPTH	PM1, PM2, PP3, PP4	0	
39	TRMU-3	c.936G>A	p.Trp312Ter	46751403G>A	Yes	PTH	PVS1, PM2	0	
40	TRMU-18, TRMU-28	c.954dup	p.Ala319ArgfsTer87	46751418-T-TC	Yes	PTH	PVS1, PM2, PP5	0.00004395	
41	TRMU-21	c.1005C>G	p.His335Gln	46751472C>G		LPTH	PM1, PM2, PP3, PP4	0	
42	TRMU-2	c.1041_1044del	p.Asn347LysfsTer7	46356008-TCAA	Yes	PTH	PVS1, PM2	0	Grover et al ⁷
43	TRMU-9, TRMU-24, TRMU-32, TRMU-39, TRMU-41	c.1073_1081dup ^b	p.Gln358_Val360dup	g.46751934_ 46751942dup		LPTH	PS3	0.00002477	Schara et al ³
44	TRMU-1	c.1081C>T	p.Arg361Cys	46751949C>T		LPTH	PM1, PM2, PP3, PP4	3.23E-5	Kerr et al ¹²
45	TRMU-12, TRMU-13	c.1084G>A	p.Ala362Thr	46751952G>A		LPTH	PM1, PM2, PP3, PP4	0	Murali et al ¹⁵
46	L-TRMU-56	c.1102-3C>G	p.?	46356839C>G	Yes	PTH	PP3, PP5, PM2	0.000007093	Uusimaa et al ⁴
47	TRMU-9	c.1108G>A	p.Val370Met	46752745G>A		LPTH	PM1, PM2, PP3, PP4	0	
48	TRMU-4, TRMU-15	c.1142G>A	p.Gly381Glu	46752779G>A		LPTH	PM1, PM2, PP3, PP4	0	Murali et al ¹⁵
49	TRMU-12, TRMU-13	del 22q13.31 46,730,453-4, 673,227			Yes				Murali et al ¹⁵

Variants presented in bold are novel.

ACMG, American College of Medical Genetics and Genomics; AMP, Association for Molecular Pathology; bp, basepair; gnomAD, Genome Aggregation Database; LoF, loss of function; LPTH, likely pathogenic; PTH, pathogenic.

^aTranscript annotation NM_001282782.

^bIndicates referred to in literature as: c.1066_1074dup (c.1073_1081dup), c.1073_1081dup, c.1081_1082insAGGCTGTGC.

Table 2 Detailed individual characteristics of all TRMU-deficient individuals in this study

Patient	Alive	Cause of Death	Age at Death (mo)	Age at First Symptoms (mo)	Age at Diagnosis (mo)	TRMU Variant 1 (NM_018006)	TRMU Variant 2 (NM_018006)	Age at Last Follow Up (mo)	Hepatic Symptoms	Number of ALF Episodes	LTX	Supplementation	Failure to thrive	Lactic Acidosis	Neuro-developmental Delay	Neuro-developmental Delay Resolved	Muscular Hypotonia	Growth Abnormality	Others	Reference	
TRMU-01	Yes			7.5	108	c.589A>C; p.Lys197Gln	c.1081C>T; p.Arg361Cys	190	x	2	No	AA	x		x	Yes		x			
TRMU-02 ^a	Yes			4	13	c.835G>A; p.Val279Met	c.1041_1044del; p.Asn347LysfsTer7	144	x	1	No	NAC								Grover et al ⁷	
TRMU-03 ^a	No	RC	6	6	8	c.835G>A; p.Val279Met	c.936G>A; p.Trp312Ter	6	x	1	No	No	x								
TRMU-04	No	HF	4	1.25	6	c.835G>A; p.Val279Met	c.1142G>A; p.Gly381Glu	4	x	1	No	No			x	Deceased					
TRMU-05 ^a	No	HF	8	0.1	pm	c.835G>A; p.Val279Met	c.248+1G>A, p?	8	x	3	Yes	NAC	x					x		Gaignard et al ¹⁵	
TRMU-06	Yes			0.1	48	c.697C>T; p.Leu233Phe	c.697C>T; p.Leu233Phe	157	x	0	No	No	x				x	x		Gaignard et al ¹⁵	
TRMU-07	Yes			2	4	c.44T>G; p.Val15Gly	c.44T>G; p.Val15Gly	107	x	1	No	NAC, Sel	x	x	x	Yes					
TRMU-08	No	MOF	7	3	4	c.40G>A; p.Gly14Ser	c.878C>T; p.Pro293Leu	7	x	1	Yes	AA, NAC		x							
TRMU-09	Yes			8	32	c.1073_1081dup; p.Gln358_Val360dup	c.1108G>A; p.Val370Met	96	x	0	No	AA	x				x				
TRMU-10	No	MOF	0.1	0.1	pm	c.664T>G; p.Cys222Gly	c.664T>G; p.Cys222Gly	0.1	x	0	No	No	x	x							
TRMU-11	Yes			4	24	c.649G>A; p.Glu217Lys	c.835G>A; p.Val279Met	120	x	0	No	No	x	x				x		Gaignard et al ¹⁵	
TRMU-12 ^a	Yes			1.5	26	c.1084G>A; p.Ala362Thr	del 22q13.31 46,730, 453-4,673,227	60	x	0	No	L-Cys, NAC	x	x	x	Yes		x		Murali et al ¹⁵	
TRMU-13 ^a	Yes			6	Fetal	c.1084G>A; p.Ala362Thr	del 22q13.31 46,730, 453-4,673,227	27	x	0	No	L-Cys, NAC		x						Murali et al ¹⁵	
TRMU-14	Yes			2	2.5	c.246C>G ^b ; p.Phe82Leu	c.525_527del; p.Phe176del	53	x	1	Yes	NAC	x	x	x	No				Murali et al ¹⁵	
TRMU-15	No	HF	3	0.5	2.5	c.1142G>A; p.Gly381Glu	c.37_48dup; p.G13_D16dup	3	x	2	No	NAC	x	x			x		Encephalopathy	Murali et al ¹⁵	
TRMU-16 ^a	Yes			1.75	2.5	c.2T>C; p.?	c.2T>C; p.?	7.5	x	3	No	L-Cys, NAC		x	x	No				Encephalopathy	
TRMU-17	No	HF		2	14	c.835G>A; p.Val279Met	c.835G>A; p.Val279Met	91	x	2	Yes	No	x	x	x	Yes		x			
TRMU-18 ^a	Yes	MOF	2	1	pm	c.954dupC; p.Ala319ArgfsTer87	c.954dupC; p.Ala319ArgfsTer87	2	0	No	No	No	x	x	x	Deceased		x		Cardiomyopathy	
TRMU-19	Yes			4	6	c.229T>C; p.Tyr77His	c.229T>C; p.Tyr77His	104	x	0	No	NAC	x		x	Yes	x	x			
TRMU-20	No	HF	3	2	pm	c.827C>T; p.Pro276Leu	c.827C>T; p.Pro276Leu	3	x	2	No	No									
TRMU-21	No	HF	3.5	0.1	pm	c.1005C>G; p.His335Gln	c.1005C>G; p.His335Gln	3.5	x	2	No	AA	x	x	x	Deceased	x				
TRMU-22	Yes			0.1	0.1	c.287A>G; p.Asn96Ser	c.287A>G; p.Asn96Ser	49	x	1	No	No	x	x	x	No		x			
TRMU-23	No	RC	1.75	1	pm	c.287A>G; p.Asn96Ser	c.287A>G; p.Asn96Ser	2	x	1	No	No	x	x	x	Deceased	x	x		Cardiomyopathy	
TRMU-24	Yes			2	NA	c.530T>A; p.Leu177His	c.1073_1081dup; p.Gln358_Val360dup	11	x	2	Yes	AA, L-Cys, NAC, Sel	x	x			x				
TRMU-25	Yes			3	0.1	c.835G>A; p.Val279Met	c.835G>A; p.Val279Met	72	x	1	No	NAC	x	x					Anemia, hyperechogenic kidneys		
TRMU-26	Yes			2	0.1	c.835G>A; p.Val279Met	c.835G>A; p.Val279Met	54	x	1	No	NAC	x								
TRMU-27	Yes			7.5	10	c.287A>G; p.Asn96Ser	c.521C>T; p.Thr174Ile	49	x	0	No	No			x	No	x				
TRMU-28 ^a	Yes			2	5	c.835G>A; p.Val279Met	c.954dup; p.Ala319ArgfsTer87	77	x	3	Yes	No	x	x	x	Lost to follow up					
TRMU-29 ^a	Yes			3	6	c.493C>A; p.Gln165Ter	c.493G>A; p.Gln165Ter	96	x	1	Yes	No									
TRMU-30 ^a	No	HF	2	0.25	1	c.117G>A; p.Trp39Ter	c.680G>C; p.Arg227Thr	2	x	1	No	No	x	x	x	Deceased		x		Encephalopathy, epileptic seizures	Soler-Alfonso et al ¹¹
TRMU-31 ^a	Yes			2	Fetal	c.117G>A; p.Trp39Ter	c.680G>C; p.Arg227Thr	45	x	1	No	AA, L-Cys, NAC, Sel		x	x	Lost to follow up	x	x			Soler-Alfonso et al ¹¹
TRMU-32	Yes			4	17	c.711_712insG; p.Gln238AlafsX14	c.1073_1081dup; p.Gln358_Val360dup	105	x	1	No	No		x							Murali et al ¹⁵
TRMU-33	Yes			1	16	c.229T>C; p.Tyr77His	c.229T>C; p.Tyr77His	157	x	1	No	No	x		x	Yes	x	x			Zeharia et al ²
TRMU-34	Yes			1.5	24	c.229T>C; p.Tyr77His	c.229T>C; p.Tyr77His	172	x	1	No	No	x					x			Zeharia et al ²
TRMU-35	Yes			4	6	c.229T>C; p.Tyr77His	c.229T>C; p.Tyr77His	93	x	1	No	NAC	x	x	x	Yes	x	x		Lower limb edema	

(continued)

Table 2 Continued

Patient	Alive	Cause of Death	Age of Death (mo)	Age at First Symptoms (mo)	Age at Diagnosis (mo)	TRMU Variant 1 (NM_018006)	TRMU Variant 2 (NM_018006)	Age at Last Follow Up (mo)	Hepatic Symptoms	Number of ALF Episodes	LTX	Supplementation	Failure to Thrive	Lactic Acidosis	Neuro-developmental Delay	Neuro-developmental Delay Resolved	Muscular Hypotonia	Growth Abnormality	Others	Reference
TRMU-36	Yes			3	3	c.229T>C; p.Tyr77His	c.229T>C; p.Tyr77His	73	x	0	No	No	x							
TRMU-37	Yes			3	120	c.229T>C; p.Tyr77His	c.229T>C; p.Tyr77His	270	x	1	No	No	x					x	Cardiomyopathy	Zeharia et al ²
TRMU-38	Yes			0.1	60	c.40G>A;p.Gly14Ser	No maternal cDNA expression	204	x	5	No	No		x					Cardiomyopathy	Zeharia et al ²
TRMU-39	Yes			0.1	1	c.653G>T; p.Ser218Ile	c.1073_1081dup; p.Gln358_Val360dup	40	x	1	No	No	x	x	x	Yes			Epileptic seizures	
TRMU-40^a	No	Sepsis	3	0.1	pm	c.339T>G; p.Tyr113Ter	c.646_648del; p.Lys216del	3	x	1	No	No	x	x	x	Deceased				
TRMU-41	Yes			2	NA	c.653G>T; p.Ser218Ile	c.1073_1081dup; p.Gln358_Val360dup	161	x	5	Yes	AA	x	x	x	Yes	x		Hypothyroidism	
TRMU-42	Yes			2	7	c.383A>G; p.Tyr128Cys	c.835G>A; p.Val279Met	45	x	1	No	AA		x			x	x	Microcephaly	Nicastro et al ¹⁰
TRMU-43	Yes			4	28	c.835G>A; p.Val279Met	c.835G>A; p.Val279Met	66	x	0	No	No		x	x	Yes				Kose et al ¹⁴
TRMU-44^a	Yes			5	6	c.581del; Gly194AspfsTer2	c.611C>T; p.Ala204Val	17	x	1	Yes	NAC	x	x				x		
TRMU-45^a	Yes			2	4.5	c.671T>G; p.Ile224Ser	c.835G>A; p.Val279Met	36	x	0	No	AA, L-Cys, NAC	x	x			x	x		
TRMU-46	No	MOF	1	0.1	pm	c.287A>G; p.Asn96Ser	c.287A>G; p.Asn96Ser	1	x	0	No	No	x	x	x	Deceased	x		Cardiomyopathy, encephalopathy	Taylor et al ⁶
TRMU-47^a	Yes			3	3	c.229T>C; p.Tyr77His	c.706-1G>A; p.?	49	x	1	Yes	NAC	x	x			x	x		
TRMU-48	Yes			2.5	78	c.229T>C; p.Tyr77His	c.229T>C; p.Tyr77His	223	x	1	Yes	NAC	x	x			x			
L-TRMU-49	No	MOF	4	3	NA	c.229T>C; p.Tyr77His	c.706-1G>A; p.?	4	x	1	No	No		x						Zeharia et al ²
L-TRMU-50	Yes			4	NA	c.229T>C; p.Tyr77His	c.229T>C; p.Tyr77His	96	x	1	No	No		x						Zeharia et al ²
L-TRMU-51	Yes			4	NA	c.229T>C; p.Tyr77His	c.229T>C; p.Tyr77His	168	x	1	No	No		x						Zeharia et al ²
L-TRMU-52	Yes			6	NA	c.815G>A; p.Gly272Asp	c.815G>A; p.Gly272Asp	24	NA	NA	No	No		x						Zeharia et al ²
L-TRMU-53 ^a	No	MOF		1	NA	c.835G>A; p.Val279Met	c.500-510del; p.Ala167GlufsTer36	2	x	1	No	No		x						Zeharia et al ²
L-TRMU-54 ^a	No	MOF	3	0.1	NA	c.2T>A; p.?	c.2T>A; p.?	3	x	NA	No	No		x						Zeharia et al ²
L-TRMU-55 ^a	No	MOF	4	0.1	NA	c.2T>A; p.?	c.2T>A; p.?	4	x	1	No	No		x						Zeharia et al ²
L-TRMU-56 ^a	Yes			5	NA	c.835G>A; p.Val279Met	c.1102-3C>G, p?	48	x	0	No	No		x			x		Bulbar involvement	Uusimaa et al ⁴
L-TRMU-57 ^a	No	RC	0.1	0.1	pm	c.34_35dup; p.Gly13ProfsTer13	c244T>G; p.Phe82Val	0.1	x	1	No	No		x			x			Qin et al ¹³
L-TRMU-58 ^a	No	HF	6	3	3	c.162_163del; p.Cys54Ter	c.680G>C; p.Arg227Thr	6	x	1	No	No	x	x	x	Deceased	x		Encephalopathy	Sala-Coromina et al ¹⁶
L-TRMU-59 ^a	No	HF	1	0.1	1	c.2T>A; p.?	c.491del; p.Leu164ProfsTer22	1	x	1	No	No	x	x	x	Deceased	x		Encephalopathy	Sala-Coromina et al ¹⁶
L-TRMU-60	Yes			3	9	c.304A>c; p.Asn102Asp	c.835G>A; p.Val279Met	60	x	1	No	No	x	x	x	Yes		x	Ichthyosis	Indolfi et al ⁸
L-TRMU-61	Yes			4	NA	c.229T>C; p.Tyr77His	c.229T>C; p.Tyr77His	NA	x	1	No	No		x					Anemia, hypothyroidism, microcephaly	Gil-Margolis et al ⁹
L-TRMU-62	Yes			5	NA	c.229T>C; p.Tyr77His	c.229T>C; p.Tyr77His	NA	x	1	No	No		x					Anemia, hypothyroidism, microcephaly	Gil-Margolis et al ⁹

Unpublished individuals are presented in bold. L-TRMU nomenclature reflects cases with only published data available. X marks the presence of a phenotypic feature.

AA, ascorbic acid; ALF, acute liver failure; cDNA, complementary DNA; HF, hepatic failure; L-cys, L-cysteine; LTX, liver transplantation; MOF, multiorgan failure; NA, not available; NAC, N-acetylcysteine; pm, post mortem; RC, respiratory and circulatory failure; Sel, selenium.

^aLoss of function variant.

^bTranscript annotation NM_001282782.

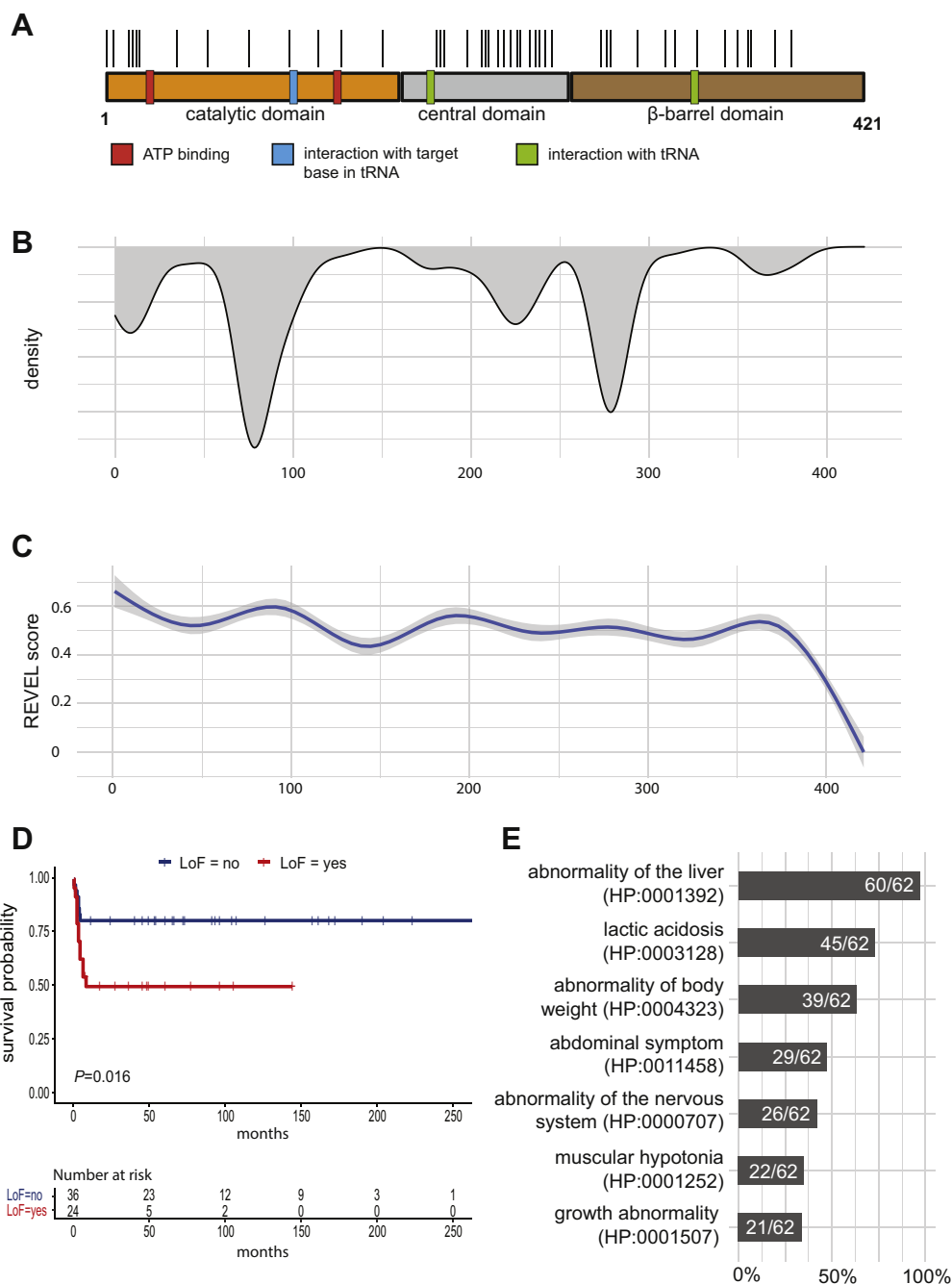


Figure 1 Genetics and clinical findings. A. All *TRMU* variants reported in this study are indicated by black lines above the corresponding amino acid position. *TRMU* protein domains and regions of important protein function are highlighted. B. Density plot of the frequency of *TRMU* variants reported in this study with respect to the affected protein domains. C. In silico pathogenicity prediction of all potential *TRMU* missense variants using REVEL score. D. LoF variants (red) influence survival probability of individuals with *TRMU* deficiency as compared with Kaplan-Meier estimate. E. Most prevalent clinical symptoms of the study cohort using Human Phenotype Ontology terminology. These include the following presentations: liver failure, cholestasis, and jaundice (abnormality of the liver); lactic acidosis; failure to thrive (abnormality of body weight), vomiting and diarrhea (abdominal symptom); motor delay, neurodevelopmental delay, and encephalopathy (abnormality of the nervous system); hypotonia (muscular hypotonia); and growth retardation (growth abnormality). ATP, adenosine triphosphate; LoF, loss of function; REVEL, rare exome variant ensemble learner; tRNA, transfer RNA.

siblings (TRMU-12 and TRMU-13), a deletion encompassing more than 1 exon in phase with a recognized missense *TRMU* variant was detected.

Variants were distributed throughout the gene (Figure 1A), with a higher density in the catalytic domain

near the site of interaction with the target base in tRNA and in the β -barrel (Figure 1B). The most frequent variants were the missense variants c.835A>G, p.(Val279Met) and c.229T>C, p.(Tyr77His), which were detected in 15 and 13 individuals, respectively. As expected, variants showed

comparable rare exome variant ensemble learner scores throughout the gene with fewer variants in the C-terminal region of the protein (Figure 1C). The 18 loss-of-function (LoF) variants and the intragenic deletion predicted to lead to loss of protein were detected at least in monoallelic state in 24 individuals. Presence of a LoF variant strongly affected on overall individual survival ($P = .016$) (Figure 1D). Overall survival did not differ between individuals having a LoF variant in 1 allele only and those having it in both alleles. ($P = .6$) (Supplemental Figure 1A).

Phenotypic spectrum

The cohort comprised 62 individuals, of whom, 42 were alive at the time of data collection (median age 6.8 years, range: 0.6-22.5 years, interquartile range [IQR] = 8.2 years). The median age of death was 3 (range: 0.1-8, IQR = 2) months. First symptoms were recognized at a median age of 2 (IQR = 3) months, and the genetic diagnosis was made at a median age of 6 months (IQR = 13.8). In 2 individuals, the diagnosis was made prenatally, both alive at inclusion, and in 9 individuals post mortem. The total duration of follow up of the cohort was 302 years, individually ranging from 0.1 to 22 (median = 3.6, IQR = 2.18) years.

The most frequent finding in all but 2 individuals (60/62, 1 NA) was liver involvement (HP:0001392). Lactic acidosis (HP:0003128, 45/62), abnormal body weight (HP:004323, 39/62, 8 NA), emesis and/or diarrhea (HP:0011458, 29/62, 8 NA), abnormality of the nervous system (HP:0000707, 26/62, 5 NA), muscular hypotonia (HP:0001252, 22/62, 5 NA), and abnormal growth (HP:0001507, 21/62, 7 NA) were further commonly reported symptoms (Figure 1E). Cause of death was most frequently reported to be multiple organ failure (8/20) or hepatic failure (8/20) (Figure 2B).

The detailed metabolic findings in blood and urine, as well as respiratory-chain enzyme activities analyzed in available tissues, did not show a specific pattern and can be found in Supplemental Table 1.

Oral supplementation of a cysteine source was reported in 40% of individuals (25/62), with NAC being most frequently used (19/25) at a median dosage of 150 (IQR = 62.5) mg/kg/d. The overall individual survival was significantly better ($P = .0052$) in individuals using any kind of cysteine supplementation than in the ones without cysteine supplementation (Figure 2A). This was even more significant ($P = .0033$) for the subgroup of 22 individuals with LoF variants (Supplemental Figure 1B).

Abnormalities of the liver (HP:0001392)

The most common hepatic feature reported was elevated hepatic transaminases (HP:0002910, 52/62, 5 NA). ALF (ORPHA: 90062), defined according to a recent consensus definition (ie, acute onset of liver disease without evidence of chronic liver disease and biochemical evidence of severe liver injury: prothrombin time of ≥ 15 seconds or international

normalized ratio of ≥ 1.5 with evidence of hepatic encephalopathy or prothrombin time of ≥ 20 seconds or international normalized ratio of ≥ 2 with or without encephalopathy²⁶), was reported in 43 of 62 (2 NA) individuals.

Further hepatic involvement included jaundice (HP:0000952, 34/62, 8 NA) and hepatomegaly (HP:0002240, 14/62, 4 NA) (Figure 2C). ALF episodes were reported earliest at age 2 weeks, peaking between age 1 and 5 months but were not reported after the first year of life (Figure 2D). Of 43 individuals with episodes of ALF, 33 had a single episode; although, recurrence of up to 5 episodes was reported (Figure 2E). Hepatic encephalopathy was reported in 13 individuals.

A total of 11 individuals received LTX, which was performed during the first episode of ALF in 4 individuals and on recurrent episodes in 6 individuals. Of note, 1 individual, who received LTX because of hepatoblastoma at age 11 years was excluded from this analysis. Median age at LTX was 4 (IQR = 1.75, range 3-10) months. There was no difference in overall individual survival based on LTX ($P = .079$) (Figure 2F). Two individuals died despite LTX: one during surgery due to variceal bleeding and the other one shortly after LTX due to multiple organ failure. Despite its benefit on overall individual survival, supplementation therapy (eg, NAC) did not avert LTX (native liver survival, $P = .24$) (Figure 3A). Analysis of hepatic biopsies, performed in 31 individuals, revealed fibrotic/cirrhotic changes of hepatic parenchyma as the most frequent finding (62%), followed by macrovesicular steatosis (41%), cholestatic changes (41%), and microvesicular steatosis (43%) (Figure 3B).

Nonhepatic phenotypic spectrum including neurodevelopmental outcome

Further commonly reported symptoms of individuals with TRMU deficiency were failure to thrive (HP:0001399, 39/62, 8 NA), neurodevelopmental delay (HP:0000707, 26/62, 9 NA), muscular hypotonia (HP:0001252, 22/62, 5 NA), growth retardation (HP:0001510, 21/62, 7 NA), and motor delay (HP:0001270, 5/62, 4 NA) (Figure 3C). Neurodevelopmental delay resolved in 11 of 26 and persisted in 4 of 26 individuals to varying extents (3/4 severe, 1/4 only motor delay persisted). Another 9 of 26 individuals were reported deceased and 2 lost to follow up (Figure 3D). In the study cohort, individuals were also reported of developing encephalopathy (HP:000129, 6/62, 4 NA), cardiomyopathy (HP:0001638, 5/62, 4 NA, follow up: 1/5 resolved, 1/5 mild left ventricular dilatation, 3/5 unknown because they deceased), epileptic seizures (HP:0001250, 4/62, 4 NA), and further rare presentations (Figure 3E).

Discussion

The list of monogenetic diseases associated with pediatric ALF is expanding owing to the increasing availability and

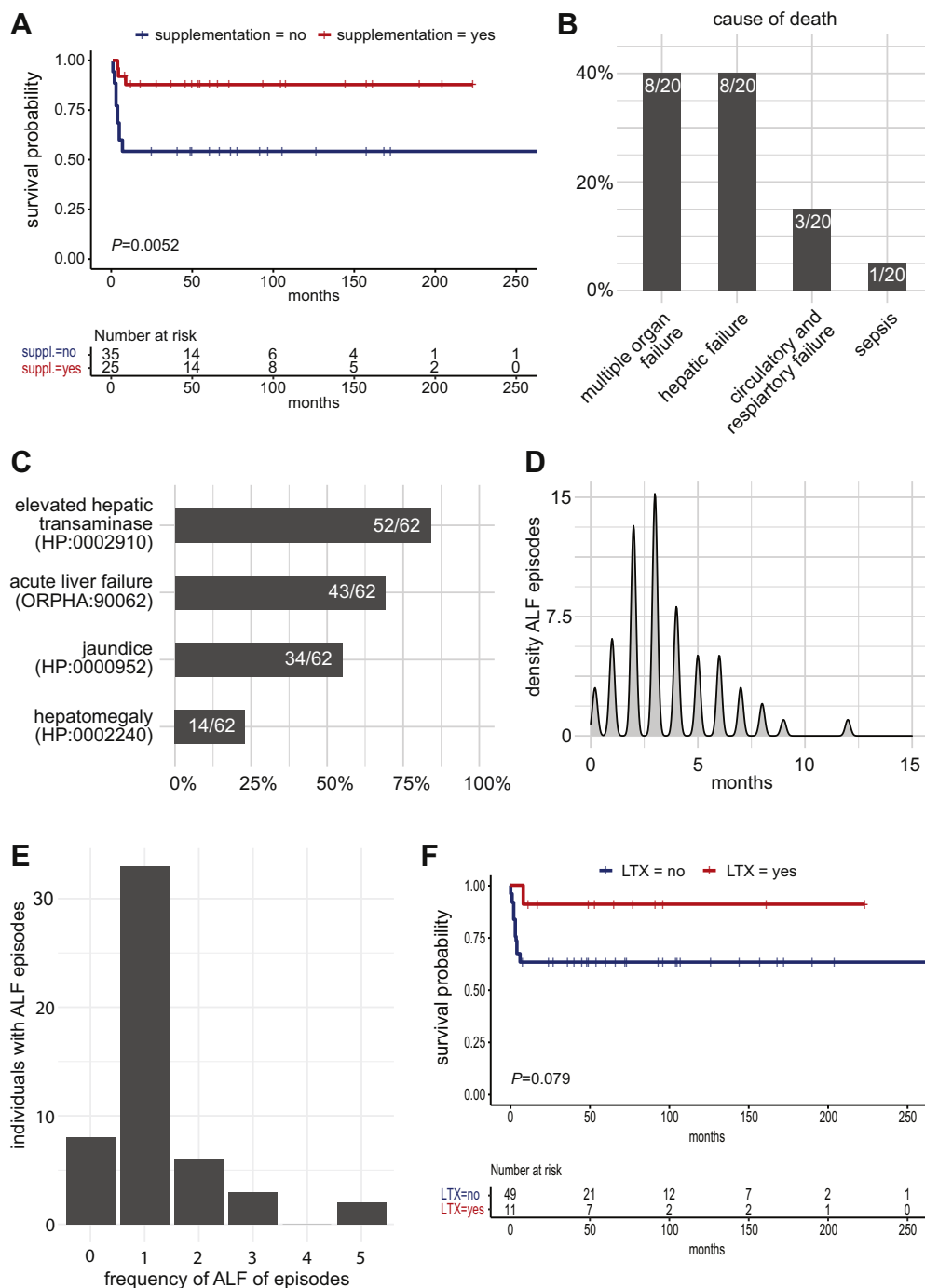


Figure 2 Individual survival and hepatic phenotype. A. Supplementation therapy (red) influences survival probability of individuals with TRMU deficiency as compared with Kaplan-Meier estimates. B. Cause of death for the 14 deceased individuals with TRMU deficiency. C. Most common features of the hepatic presentation of individuals with TRMU deficiency. D. Density plot indicating the occurrence of ALF episodes over the first 15 months of life. E. Frequency of ALF episodes per individual across the cohort. F. Survival probability of individuals with TRMU deficiency with LTX therapy (red) and without LTX therapy (blue) is compared using Kaplan-Meier estimator. ALF, acute liver failure; LTX, liver transplantation.

applicability of next-generation sequencing technologies. Within this patient group, pathogenic variants in genes pivotal for mitochondrial function are separately recognized because ALF can be the first symptom of a future multiorgan disease. Particularly, the risk of coexisting cardiomyopathy and cerebral involvement must be excluded when LTX is considered

as rescue therapy for ALF. TRMU-associated ALF has been first described in 13 individuals in 2009.² Subsequently, another 23 cases were described.³⁻¹⁶

This study presents the largest reported cohort of 62 individuals with TRMU deficiency, summarizing the initial clinical presentations and long-term clinical course as well

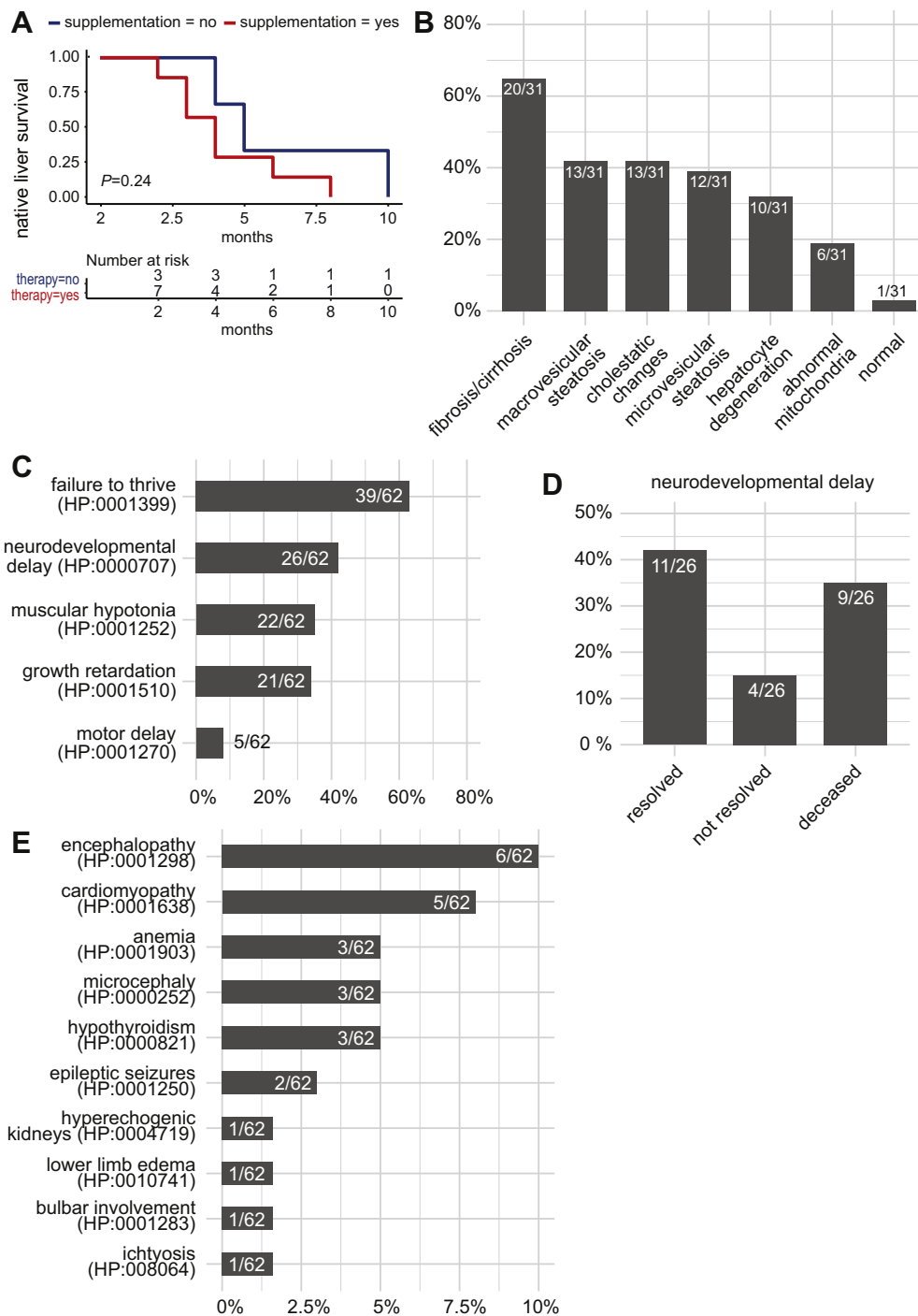


Figure 3 Native liver survival, liver histology, clinical presentation, and course of TRMU-related symptoms. A. Supplementation therapy (blue) does not influence native liver survival, ie, the need for liver transplantation, as compared with Kaplan-Meier estimates. B. Most prevalent findings in liver histopathology. C. Common clinical presentation of individuals with TRMU deficiency besides hepatic symptoms. D. Course of individuals with neurodevelopmental delay over time. Note, that 1 individual was lost to follow up. E. Less common clinical findings in individuals with TRMU deficiency.

as all variants in *TRMU* associated with the disease. Still, cohort heterogeneity, sample size, and the retrospective nature of this study may limit the conclusions that can be drawn from the data analysis.

In translating our study results to practical, evidence-based recommendations, eg, when informing parents or

setting up a treatment plan with the medical team for a newly diagnosed individual with TRMU deficiency, we can conclude that in most (40/62, 65%) individuals, TRMU-associated ALF is indeed a transient, reversible disease. Unfortunately, however, it led to death in more than a third of the affected individuals. Presence of LoF variants was a

negative predictor for overall individual survival (Figure 1D). Furthermore, in this cohort, no episodes of ALF occurred after the first year of life.

A possible explanation for this temporal presentation of ALF was provided recently by the demonstration that over the first year of life, some mitochondrial defects (including TRMU) can be metabolically compensated for by the activation of the cellular stress response and mTOR associated mitochondrial biogenesis.²⁷ This would support the hypothesis of cysteine supplementation therapy, which has shown benefits in anecdotal cases of TRMU deficiency disease.^{11,15} Indeed, we found that supplementation with at least 1 cysteine source, NAC being the most frequently used in our cohort, improved survival significantly (level of evidence 1c, Figure 2A, survival probability in the first year with supplementation: 90%, without: 50%), particularly in the subgroup of individuals with predicted loss of protein function.

Consequently, it is an evidence-based medicine level 1c recommendation to supplement with a cysteine source in any patient with TRMU deficiency at least in the first year. We further recommend considering NAC as the primary cysteine source given that it is thought to provide extended benefits for failing liver tissue by compensating for redox dysfunction (as commonly used in paracetamol-induced liver failure). We would further encourage consideration of supplementing NAC to all cases of suspected mitochondrial liver failure until TRMU-related disease has been excluded. However, conclusions on which cysteine source is the best and dosing and duration of supplementation cannot be drawn owing to the limited data availability. Further research is required to better understand the underlying pathophysiology and possible treatment options.

On theoretical grounds, supplementation may only be necessary up to age 1 year. Interestingly, native liver survival (Figure 2F) seems unaffected by supplementation and the occurrence of ALF under supplementation may still require LTX because once the catastrophic cascade of hepatic necrosis is initiated, it seems not to be ameliorated by adding a cysteine sources. One could speculate that an earlier diagnosis and a consecutively early cysteine supplementation might improve outcome. We cannot arrive to a final conclusion based on our limited data. However, the survival of 2 individuals, diagnosed prenatally, who received early supplementation with cysteine suggests that this approach may lead to a better outcome.

The decisions regarding necessity and timing of LTX remain specific to the clinical circumstances, but the fact that no ALF was reported after the age 1 year should be considered. Alternatively, progression of established ALF and worsening of hepatic encephalopathy with associated cerebral injury will eventually necessitate LTX.

TRMU deficiency is predominantly a disease of the first year of life. Our cohort yielded multiorgan involvements but only in a minority of patients (Figure 3E). However, the most commonly reported during follow up in our cohort was neurodevelopmental delay. It is impossible to determine to what extent the neurodevelopmental delay is secondary to

the liver failure or an unrelated clinical expression of mitochondrial disease. This also holds for the brain magnetic resonance imaging finding of bilateral hyperintensities in the basal ganglia as described in the article by Sala-Coromina et al.¹⁶ These were reported during ALF in 2 patients who died shortly afterwards. Hence, it is impossible to ascertain that this magnetic resonance imaging finding reflects the imaging of a vulnerable brain with mitochondrial dysfunction or whether this child would have progressed to the full picture of Leigh syndrome (subacute necrotizing encephalomyelopathy) in the strictest sense.²⁸

Given the rarity of TRMU deficiency, we advise that generally, there should be careful follow up of individuals in the first year by an experienced team at a specialized center with pediatric liver and mitochondrial disease specialists. Extended but regular follow-up visits with ultrasound examination of the liver and biochemical surveillance, including alpha-fetoprotein levels, should also exceed the first year of life. Furthermore, where clinically and genetically indicated, active consideration of LTX seems advisable.

Data Availability

Data will be supplied by the authors upon request.

Acknowledgments

The Chair in Genomic Medicine awarded to J.C. is generously supported by The Royal Children's Hospital-Foundation The Royal Children's Hospital Foundation. We are grateful to the Crane, Perkins, and Miller families for their generous financial support. We thank the Kinghorn Centre for Clinical Genomics for assistance with production and processing of genome sequencing data. This project was supported by the funding from MitoCanada (<https://mitocanada.org>) as part of the Mitochondrial Functional and Integrative Next Generation Diagnostics (MITO-FIND) study. This work was supported by the European Reference Network for Hereditary Metabolic Disorders (MetabERN). S.W. received funding from ERAPERMED2019-310 Personalized Mitochondrial Medicine (PerMiM): Optimizing diagnostics and treatment for patients with mitochondrial diseases FWF 4704-B. F.S.A. is funded by the National Institutes of Health along with the North American Mitochondrial Disease Consortia (5U54-NS078059-11), the Frontiers of Congenital Disorders of Glycosylation Consortia (FCDGC, 5U54-NS115198-02), Mervar Foundation, Courage for a Cure Foundation, PTC Therapeutics, Astellas Pharma Inc, and Saol Therapeutics. R.M. and R.W.T. are funded by the Wellcome Trust Centre for Mitochondrial Research (203105/Z/16/Z), the Mitochondrial Disease Patient Cohort (United Kingdom) (G0800674), the Medical Research Council International Centre for Genomic

Medicine in Neuromuscular Disease (MR/S005021/1), the Medical Research Council (MR/W019027/1), the Lily-Foundation, the UK NIHR Biomedical Research Centre for Ageing and Age-related Disease award to the Newcastle upon Tyne Hospitals NHS Foundation Trust, and the UK NHS Highly Specialised Service for Rare Mitochondrial Disorders of Adults and Children. R.W.T. also receives funding from the Pathological Society of Great Britain and Ireland. J.C. is supported by a New South Wales Office of Health and Medical Research Council Sydney Genomics Collaborative grant. We acknowledge funding from the National Health and Medical Research Council (NHMRC): project grant GNT1164479 (D.R.T.) and Principal Research Fellowship GNT1155244 (D.R.T.). The research conducted at the Murdoch Children's Research Institute was supported by the Victorian Government's Operational Infrastructure Support program. This study was supported by BMBF (German Federal Ministry of Education and Research) through the German Network for Mitochondrial Diseases ([mitoNET] grant number 01GM1906B), Personalized Mitochondrial Medicine (PerMiM) (grant number 01KU2016A), and E-Rare project GENOMIT (grant number 01GM1207) and the Bavarian State Ministry of Health and Care within its framework of DigiMed Bayern (grant number DMB-1805- 0002). The authors extend their appreciation to the King Salman Center For Disability Research for funding this work through research group number RG-2022-010 (to F.S.A.)

Author Information

Conceptualization: G.F.V., S.W.; Data Curation: G.F.V., S.W., Y.M.-G., Y.E.L., R.G.F., J.A.M., H.B., L.D.S., H.Pr., A.Pec., F.S.A., J.J.B., G.B., I.B., N.B., B.B., J.C., E.C., D.C., A.M.D., N.D., A.D.M., F.D., E.A.E., M.E., W.F., P.G., R.D.G., E.G., C.H., J.H., V.K., M.Ko., M.Ke., A.K., D.L., R.M., M.G.M., K.Mo., T.M., K.Mu., E.N., A.Pen., H.Pe., D.P.-A., A.R., R.S., F.S., M.Sc., M.Shag., M.Shar., C.S.-A., C.S., I.S., M.St., R.W.T., D.R.T., E.L.T., J.-S.W., D.W.; Methodology: G.F.V., S.W., R.G.F., J.A.M.; Visualization: G.F.V., S.W., H.B., J.S.; Writing-original draft: G.F.V., S.W.; Writing-review and editing: G.F.V., S.W., Y.M.-G., Y.E.L., R.G.F., J.A.M., H.B., L.D.S., H.Pr., A.Pec., F.S.A., J.J.B., G.B., I.B., N.B., B.B., J.C., E.C., D.C., A.M.D., N.D., A.D.M., F.D., E.A.E., M.E., W.F., P.G., R.D.G., E.G., C.H., J.H., V.K., M.Ko., M.Ke., A.K., D.L., R.M., M.G.M., K.Mo., T.M., K.Mu., E.N., A.Pen., H.Pe., D.P.-A., A.R., R.S., F.S., M.Sc., M.Shag., M.Shar., C.S.-A., C.S., I.S., M.St., R.W.T., D.R.T., E.L.T., J.-S.W., D.W.

Ethics Declaration

This study was conducted in accordance with the guidelines of the Institutional Review Board of the Medical University

of Innsbruck and the 1975 Declaration of Helsinki.²⁹ Participants gave written informed consent for genetic investigations according to local regulations.

Conflict of Interest

The authors declare no conflicts of interest.

Additional Information

The online version of this article (<https://doi.org/10.1016/j.gim.2022.09.015>) contains supplementary material, which is available to authorized users.

Authors

Georg F. Vogel^{1,2,*} , Yael Mozer-Glassberg³, Yuval E. Landau^{4,5}, Lea D. Schlieben^{6,7}, Holger Prokisch^{6,7}, René G. Feichtinger⁸, Johannes A. Mayr⁸, Heiko Brennenstuhl^{9,10}, Julian Schröter¹¹, Agnes Pechlaner¹, Fowzan S. Alkuraya¹², Joshua J. Baker¹³, Giulia Barcia^{14,15}, Ivo Baric¹⁶, Nancy Braverman¹⁷, Birute Burnyte¹⁸, John Christodoulou^{19,20}, Elzbieta Ciara²¹, David Coman²², Anibh M. Das²³, Niklas Darin²⁴, Adela Della Marina²⁵, Felix Distelmaier²⁶, Erik A. Eklund²⁷, Melike Ersoy²⁸, Weiyang Fang²⁹, Pauline Gaignard³⁰, Rebecca D. Ganetzky^{31,32}, Emmanuel Gonzales^{33,34}, Caoimhe Howard³⁵, Joanne Hughes³⁵, Vassiliki Konstantopoulou³⁶, Melis Kose^{37,38}, Marina Kerr³⁹, Aneal Khan³⁹, Dominic Lenz⁹, Robert McFarland^{40,41}, Merav Gil Margolis⁴², Kevin Morrison⁴³, Thomas Müller¹, Kei Murayama⁴⁴, Emanuele Nicastro⁴⁵, Alessandra Pennisi^{14,15}, Heidi Peters⁴⁶, Dorota Piekutowska-Abramczuk²¹, Agnès Rötig¹⁵, René Santer⁴⁷, Fernando Scaglia^{48,49,50}, Manuel Schiff^{14,15,51}, Mohmmad Shagrani^{52,53}, Mark Sharrard⁵⁴, Claudia Soler-Alfonso⁴⁸, Christian Staufner⁹, Imogen Storey⁵⁵, Michael Stormon⁵⁶, Robert W. Taylor^{40,41}, David R. Thorburn^{19,20}, Elisa Leao Teles⁵⁷, Jian-She Wang²⁹, Daniel Weghuber⁸, Saskia Wortmann^{8,58}

Affiliations

¹Department of Paediatrics I, Medical University of Innsbruck, Innsbruck, Austria; ²Institute of Cell Biology, Biocenter, Medical University of Innsbruck, Innsbruck, Austria; ³Institute for Gastroenterology, Nutrition and Liver diseases, Schneider Children's Medical Center of Israel, Petah Tiqwa, Israel; ⁴Metabolism Service, Schneider Children's Medical

Center of Israel, Petah Tiqwa, Israel; ⁵Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; ⁶Institute of Human Genetics, School of Medicine, Technical University of Munich, Munich, Germany; ⁷Institute of Neurogenomics, Computational Health Center, Helmholtz Zentrum München, Neuherberg, Germany; ⁸University Children's Hospital, Salzburger Landeskliniken and Paracelsus Medical University, Salzburg, Austria; ⁹Division of Neuropaediatrics and Paediatric Metabolic Medicine, Center for Paediatric and Adolescent Medicine, University Hospital Heidelberg, Heidelberg, Germany; ¹⁰Institute of Human Genetics, Heidelberg University, Heidelberg, Germany; ¹¹Division of Paediatric Epileptology, Center for Paediatric and Adolescent Medicine, University Hospital Heidelberg, Heidelberg, Germany; ¹²Department of Genetics, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia; ¹³Division of Genetics, Birth Defects and Metabolism, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL; ¹⁴Department of Medical Genetics and Reference Center for Mitochondrial Diseases (CAR-AMMEL), Necker Hospital, Université Paris Cité, Paris, France; ¹⁵Institut Imagine, INSERM UMR 1163, Paris, France; ¹⁶Department of Pediatrics, School of Medicine, University Hospital Center Zagreb and University of Zagreb, Zagreb, Croatia; ¹⁷Division of Medical Genetics, Department of Pediatrics and Human Genetics, McGill University, Montreal, Quebec, Canada; ¹⁸Department of Human and Medical Genetics, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; ¹⁹Brain and Mitochondrial Research Group, Murdoch Children's Research Institute, Melbourne, Victoria, Australia; ²⁰Department of Paediatrics, The University of Melbourne, Melbourne, Victoria, Australia; ²¹Department of Medical Genetics, The Children's Memorial Health Institute, Warsaw, Poland; ²²Faculty of Medicine, Queensland Children's Hospital, University of Queensland, Herston, Brisbane, Queensland, Australia; ²³Department of Paediatrics, Paediatric Metabolic Medicine, Hannover Medical School, Hannover, Germany; ²⁴Department of Pediatrics, Institute of Clinical Sciences, University of Gothenburg, Gothenburg, Sweden; ²⁵Department of Pediatric Neurology, Centre for Neuromuscular Disorders, Centre for Translational Neuro- und Behavioral Sciences, University Duisburg-Essen, Essen, Germany; ²⁶Department of General Pediatrics, Neonatology and Pediatric Cardiology, Medical Faculty, Heinrich-Heine-University Dusseldorf, Dusseldorf, Germany; ²⁷Section for Pediatrics, Department of Clinical Sciences, Lund University, Lund, Sweden; ²⁸Department of Pediatrics, Division of Pediatric Metabolism, University of Health Sciences, Bakirkoy Dr. Sadi Konuk Training and Research, Istanbul, Turkey; ²⁹The Center for Pediatric Liver Diseases, Children's Hospital of Fudan University, National Children's Medical Center, Shanghai, China; ³⁰Department of Biochemistry, Reference Center for Mitochondrial Disease, FILNEMUS, Bicêtre University Hospital, University of Paris-Saclay, Assistance Publique-Hôpitaux de Paris, Le

Kremlin-Bicêtre, Paris, France; ³¹Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; ³²Mitochondrial Medicine Frontier Program, Division of Human Genetics, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA; ³³Pediatric Hepatology and Pediatric Liver Transplantation Unit, Reference Center for Mitochondrial Disease, FILNEMUS, Bicêtre University Hospital, University of Paris-Saclay, Assistance Publique-Hôpitaux de Paris, Le Kremlin-Bicêtre, Paris, France; ³⁴Inserm U1193, Hepatov, University Paris-Saclay, Orsay, Paris, France; ³⁵Children's Health Ireland, Temple Street Hospital, Dublin, Ireland; ³⁶Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria; ³⁷Division of Inborn Errors of Metabolism, Department of Pediatrics, İzmir Katip Çelebi University, Izmir, Turkey; ³⁸Division of Genetics, Department of Pediatrics, Ege University, Izmir, Turkey; ³⁹Discovery DNA, Metabolics and Genetics in Canada (M.A.G.I.C.) Clinic Ltd, Department of Pediatrics, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada; ⁴⁰Wellcome Centre for Mitochondrial Research, Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom; ⁴¹NHS Highly Specialised Service for Rare Mitochondrial Disorders, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom; ⁴²Institute of Endocrinology and Diabetes, National Center of Childhood Diabetes Schneider Children's Medical Center of Israel, Petah Tiqwa, Israel; ⁴³Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL; ⁴⁴Department of Metabolism, Chiba Children's Hospital, Midori-ku, Chiba, Japan; ⁴⁵Pediatric Hepatology, Gastroenterology and Transplantation, Hospital Papa Giovanni XXIII, Bergamo, Italy; ⁴⁶Department of Metabolic Medicine, Royal Children's Hospital, Melbourne, Victoria, Australia; ⁴⁷Department of Pediatrics, University Medical Center Hamburg Eppendorf, Hamburg, Germany; ⁴⁸Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX; ⁴⁹Texas Children's Hospital, Houston, TX; ⁵⁰Joint BCM-CUHK Center of Medical Genetics, Prince of Wales Hospital, Shatin, Hong Kong SAR; ⁵¹Reference Center of Inherited Metabolic Disorders, Necker Hospital, Université Paris Cité, Paris, France; ⁵²Department of Liver & Small Bowel Health Centre King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia; ⁵³College of Medicine, Alfaisal University, Riyadh, Saudi Arabia; ⁵⁴Sheffield Children's NHS Foundation Trust, Sheffield, United Kingdom; ⁵⁵University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; ⁵⁶Department of Gastroenterology, The Children's Hospital at Westmead, Sydney, New South Wales, Australia; ⁵⁷Inherited Metabolic Diseases Reference Centre, São João Hospital University Centre, EPE, Porto, Portugal; ⁵⁸Amalia Children's Hospital, Radboudumc, Nijmegen, The Netherlands

References

- Narkewicz MR, Horslen S, Hardison RM, et al. A learning collaborative approach increases specificity of diagnosis of acute liver failure in pediatric patients. *Clin Gastroenterol Hepatol*. 2018;16(11):1801-1810.e3. <http://doi.org/10.1016/j.cgh.2018.04.050>
- Zeharia A, Shaag A, Pappo O, et al. Acute infantile liver failure due to mutations in the TRMU gene. *Am J Hum Genet*. 2009;85(3):401-407. Published correction appears in *Am J Hum Genet*. 2010;86(2):295. <https://doi.org/10.1016/j.ajhg.2009.08.004>
- Schara U, von Kleist-Retzow JC, Lainka E, et al. Acute liver failure with subsequent cirrhosis as the primary manifestation of TRMU mutations. *J Inherit Metab Dis*. 2011;34(1):197-201. <http://doi.org/10.1007/s10545-010-9250-z>
- Uusimaa J, Jungbluth H, Fratter C, et al. Reversible infantile respiratory chain deficiency is a unique, genetically heterogeneous mitochondrial disease. *J Med Genet*. 2011;48(10):660-668. <http://doi.org/10.1136/jmg.2011.089995>
- Gaignard P, Gonzales E, Ackermann O, et al. Mitochondrial infantile liver disease due to TRMU gene mutations: three new cases. *JIMD Rep*. 2013;11:117-123. http://doi.org/10.1007/8904_2013_230
- Taylor RW, Pyle A, Griffin H, et al. Use of whole-exome sequencing to determine the genetic basis of multiple mitochondrial respiratory chain complex deficiencies. *JAMA*. 2014;312(1):68-77. <http://doi.org/10.1001/jama.2014.7184>
- Grover Z, Lewindon P, Clouston A, Shaag A, Elpeleg O, Coman D. Hepatic copper accumulation: a novel feature in transient infantile liver failure due to TRMU mutations? *JIMD Rep*. 2015;21:109-113. http://doi.org/10.1007/8904_2014_402
- Indolfi G, Iacone M, Remaschi G, et al. A child with ichthyosis and liver failure. *J Pediatr Gastroenterol Nutr*. 2017;65(3):e70-e73. <http://doi.org/10.1097/MPG.0000000000001645>
- Gil-Margolis M, Mozer-Glassberg Y, Tobar A, Ashkenazi S, Zeharia A, Marom D. [TRMU mutations – reversible infantile liver failure or multisystem disorder?] *Harefuah*. 2018;157(1):52-57.
- Nicastro E, Di Giorgio A, Marchetti D, et al. Diagnostic yield of an algorithm for neonatal and infantile cholestasis integrating next-generation sequencing. *J Pediatr*. 2019;211:54-62.e4. <http://doi.org/10.1016/j.jpeds.2019.04.016>
- Soler-Alfonso C, Pillai N, Cooney E, Mysore KR, Boyer S, Scaglia F. L-cysteine supplementation prevents liver transplantation in a patient with TRMU deficiency. *Mol Genet Metab Rep*. 2019;19:100453. <http://doi.org/10.1016/j.ymgmr.2019.100453>
- Kerr M, Hume S, Omar F, et al. MITO-FIND: A study in 390 patients to determine a diagnostic strategy for mitochondrial disease. *Mol Genet Metab*. 2020;131(1-2):66-82. <http://doi.org/10.1016/j.ymgme.2020.08.009>
- Qin Z, Yang Q, Yi S, Huang L, Shen Y, Luo J. Whole-exome sequencing identified novel compound heterozygous variants in a Chinese neonate with liver failure and review of literature. *Mol Genet Genomic Med*. 2020;8(12):e1515. <http://doi.org/10.1002/mgg3.1515>
- Kose M, Isik E, Aykut A, et al. The utility of next-generation sequencing technologies in diagnosis of Mendelian mitochondrial diseases and reflections on clinical spectrum. *J Pediatr Endocrinol Metab*. 2021;34(4):417-430. <http://doi.org/10.1515/jpem-2020-0410>
- Murali CN, Soler-Alfonso C, Loomes KM, et al. TRMU deficiency: A broad clinical spectrum responsive to cysteine supplementation. *Mol Genet Metab*. 2021;132(2):146-153. <http://doi.org/10.1016/j.ymgme.2021.01.005>
- Sala-Coromina J, Miguel LD, de Las Heras J, et al. Leigh syndrome associated with TRMU gene mutations. *Mol Genet Metab Rep*. 2020;26:100690. <http://doi.org/10.1016/j.ymgmr.2020.100690>
- Sturman JA, Gaull G, Raiha NC. Absence of cystathionase in human fetal liver: is cystine essential? *Science*. 1970;169(3940):74-76. <http://doi.org/10.1126/science.169.3940.74>
- Ferreira CR, Rahman S, Keller M, Zschocke J, ICIMD Advisory Group. An international classification of inherited metabolic disorders (ICIMD). *J Inherit Metab Dis*. 2021;44(1):164-177. <http://doi.org/10.1002/jimd.12348>
- Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-424. <http://doi.org/10.1038/gim.2015.30>
- Köhler S, Gargano M, Matentzoglou N, et al. The Human Phenotype Ontology in 2021. *Nucleic Acids Res*. 2021;49(D1):D1207-D1217. <http://doi.org/10.1093/nar/gkaa1043>
- Ioannidis NM, Rothstein JH, Pejaver V, et al. REVEL: an Ensemble method for predicting the pathogenicity of rare missense variants. *Am J Hum Genet*. 2016;99(4):877-885. <http://doi.org/10.1016/j.ajhg.2016.08.016>
- Jagadeesh KA, Wenger AM, Berger MJ, et al. M-CAP eliminates a majority of variants of uncertain significance in clinical exomes at high sensitivity. *Nat Genet*. 2016;48(12):1581-1586. <http://doi.org/10.1038/ng.3703>
- Vaser R, Adusumalli S, Leng SN, Sikic M, Ng PC. SIFT missense predictions for genomes. *Nat Protoc*. 2016;11(1):1-9. <http://doi.org/10.1038/nprot.2015.123>
- Hebebrand M, Hüffmeier U, Trollmann R, et al. The mutational and phenotypic spectrum of TUBA1A-associated tubulinopathy. *Orphanet J Rare Dis*. 2019;14(1):38. <http://doi.org/10.1186/s13023-019-1020-x>
- Lenz D, Smith DEC, Crushell E, et al. Genotypic diversity and phenotypic spectrum of infantile liver failure syndrome type 1 due to variants in LARS1. *Genet Med*. 2020;22(11):1863-1873. <http://doi.org/10.1038/s41436-020-0904-4>
- Squires JE, Alonso EM, Ibrahim SH, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition position paper on the diagnosis and management of pediatric acute liver failure. *J Pediatr Gastroenterol Nutr*. 2022;74(1):138-158. <http://doi.org/10.1097/MPG.0000000000003268>
- Hathazi D, Griffin H, Jennings MJ, et al. Metabolic shift underlies recovery in reversible infantile respiratory chain deficiency. *EMBO J*. 2020;39(23):e105364. <http://doi.org/10.15252/embj.2020105364>
- Rahman S, Thorburn D. Nuclear gene-encoded Leigh syndrome spectrum overview. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews [Internet]*. University of Washington: Seattle; 1993-2022.
- World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. <http://doi.org/10.1001/jama.2013.281053>