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ARTICLE

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

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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.

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

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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 disorder[18]). 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.3.5a[21-23]) 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 smoothened 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 published[2-16] (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	LoF	ACMG/AMP Rating	Details of ACMG/AMP Rating	gnomAD Allele Frequency	Reference
1	**TRMU-16**	**c.2T>C**	**p.?**	**46335766T>C**	**Yes**	**PTH**	**PVS1, PM2, PP5**	**0**	
2	L-TRMU-54, L-TRMU-55, L-TRMU-59	c.2T>A	p.?	46335766T>C	Yes	PTH	PVS1, PP5, PM2	0	Zeharia et al,[2] Sala-Coromina et al[16]
3	L-TRMU-57	c.34_35dup	p.Gly13ProfsTer13	46335798–TC	Yes	LPTH	PVS1, PM2	0	Qin et al[13]
4	TRMU-15	c.37_48dup	p.Gly_Asp16dup	chr22-46335800 –CG…GA (12 bp)		LPTH	PM2, PM4, PP3	0.00003575	Murali et al[15]
5	TRMU-8, TRMU-38	c.40G>A	p.Gly14Ser	46731701G>A		LPTH	PS3, PM1, PP3, PP4	6.47E-5	Zeharia et al[2]
6	**TRMU-7**	**c.44T>G**	**p.Val15Gly**	**46731705T>G**		**LPTH**	**PM1, PM2, PP3, PP4**	**0**	
7	TRMU-30, TRMU-31	c.117G>A	p.Trp39Ter	46733710G>A	Yes	PTH	PP5, PVS1, PM2	0	Soler-Alfonso et al,[11] Murali et al[15]
8	L-TRMU-58	c.162_163del	p.Cys54Ter	46337856-TG	Yes	PTH	PVS1, PM2	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	PM1, PM2, PP3, PP4, PP5	0	Zeharia et al,[2] Gil-Margolis et al[9]
10	L-TRMU-57	c.244T>G	p.Phe82Val	46733837T>G		LPTH	PM1, PM2, PM3, PP4	0	Qin et al[13]
11	TRMU-14	c.246C>G[a]	p.Phe82Leu	46337942C>G		LPTH	PM1, PM2, PP3, PP4	0	Murali et al[15]
12	TRMU-5	c.248+1G>A	p.?	46337945G>A	Yes	PTH	PVS1, PM2	0	Gaignard et al[5]
13	TRMU-22, TRMU-23, TRMU-27, TRMU-46	c.287A>G	p.Asn96Ser	46739197A>G		LPTH	PM1, PM2, PP3, PP4	0	Taylor et al[6]
14	L-TRMU-60	c.304A>G	p.Asn102Asp	46343317A>G		LPTH	PM2, PP3, PP5	0	Indolfi et al[8]
15	**TRMU-40**	**c.339T>G**	**p.Tyr113Ter**	**46739249T>G**	**Yes**	**PTH**	**PVS1, PM2, PP4**	**0**	
16	TRMU-42	c.383A>G	p.Tyr128Cys	46742346A>G		LPTH	PM1, PM2, PP3, PP4	0	Nicastro et al[10]
17	L-TRMU-59	c.491del	p.Leu164ProfsTer22	46350303-T	Yes	LPTH	PV1, PM2	0	Sala-Coromina et al[16]
18	**TRMU-29**	**c.493C>A**	**p.Gln165Ter**	**46746202G>A**	**Yes**	**PTH**	**PVS1, PM2**	**0**	
19	L-TRMU-53	c.500_510del	p.Ala167GlufsTer36	46350312-CT…TT (11 bp)	Yes	PTH	PV1, PM2	0	Zeharia et al[2]
20	**TRMU-27**	**c.521C>T**	**p.Thr174Ile**	**46746230C>T**		**LPTH**	**PM1, PM2, PP3, PP4**	**0**	
21	TRMU-14	c.525_527del	p.Phe176del	46350334-CTT		LPTH	PM2, PM4, PP3, PP5	0.00001193	Murali et al[15]
22	**TRMU-24**	**c.530T>A**	**p.Leu177His**	**46746239T>A**		**LPTH**	**PM1, PM2, PP3, PP4**	**0**	
23	**TRMU-44**	**c.581del**	**p.Gly194AspfsTer2**	**46746284-TG-T**	**Yes**	**PTH**	**PVS1, PM2, PP5**	**0.00002475**	
24	TRMU-1	c.589A>C	p.Lys197Gln	46746298A>C		LPTH	PM1, PM2, PP3, PP4	0	Kerr et al[12]
25	**TRMU-44**	**c.611C>T**	**p.Ala204Val**	**46746320C>T**		**LPTH**	**PM1, PM2, PP3, PP4**	**0**	
26	**TRMU-40**	**c.646_648del**	**p.Lys216del**	**46350458-AAA**		**LPTH**	**PM2, PM4, PP3**	**0**	
27	TRMU-11	c.649G>A	p.Glu217Lys	46746358G>A		LPTH	PM1, PM2, PP3, PP4	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.

[a]Transcript annotation NM_001282782.

[b]Indicates 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 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-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[5]
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[5]
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[5]
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	Yes			2	14	c.835G>A; p.Val279Met	c.835G>A; p.Val279Met	91	x	2	Yes	No	x		x	Yes		x		
TRMU-18[a]	No	MOF	2	1	pm	c.954dupC; p.Ala319ArgfsTer87	c.954dup; p.Ala319ArgfsTer87	2		0	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	x					x		
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] Murali et al[15]
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] Murali et al[15]
TRMU-32	Yes			4	17	c.711_712insG; p.Gln238AlafsX14	c.1073_1081dup; p.Gln358_Val360dup	105	x	1	No	No		x						Schara et al[3]
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					x		
TRMU-37	Yes			3	120	c.229T>C; p.Tyr77His	c.229T>C; p.Tyr77His	270	x	1	No	No	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		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			Microcephaly	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			
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 involvment	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			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	Ichtyosis	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.

[a]Loss of function variant.

[b]Transcript annotation NM_001282782.

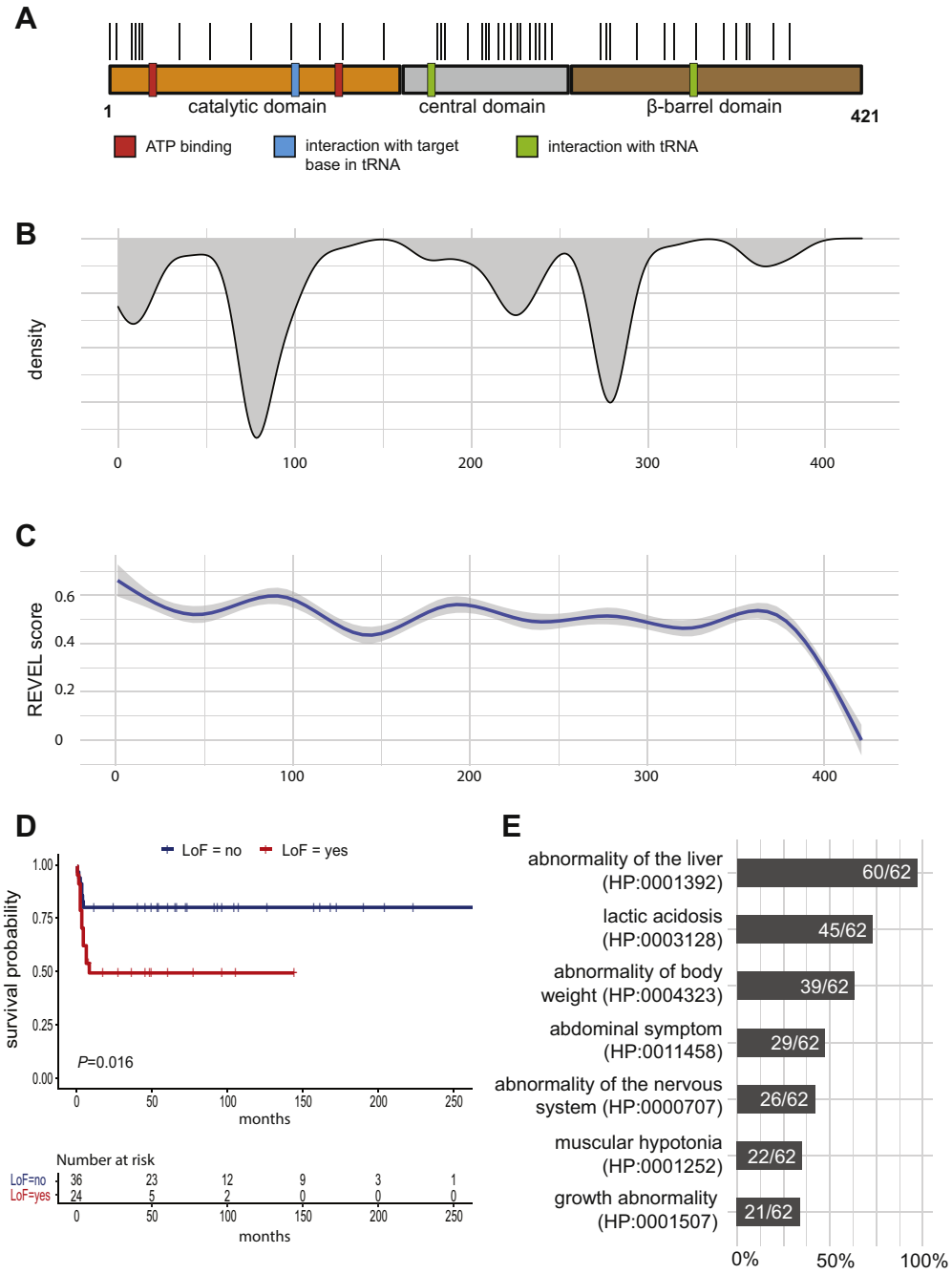

Figure 1 **Genetics and clinical findings.** A. All *TRMU* variants reported in this study are indicated by black lines above the corresponding amino acid position. TRMU protein domains and regions of important protein function are highlighted. B. Density plot of the frequency of *TRMU* variants reported 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 encephalopathy[26]), 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

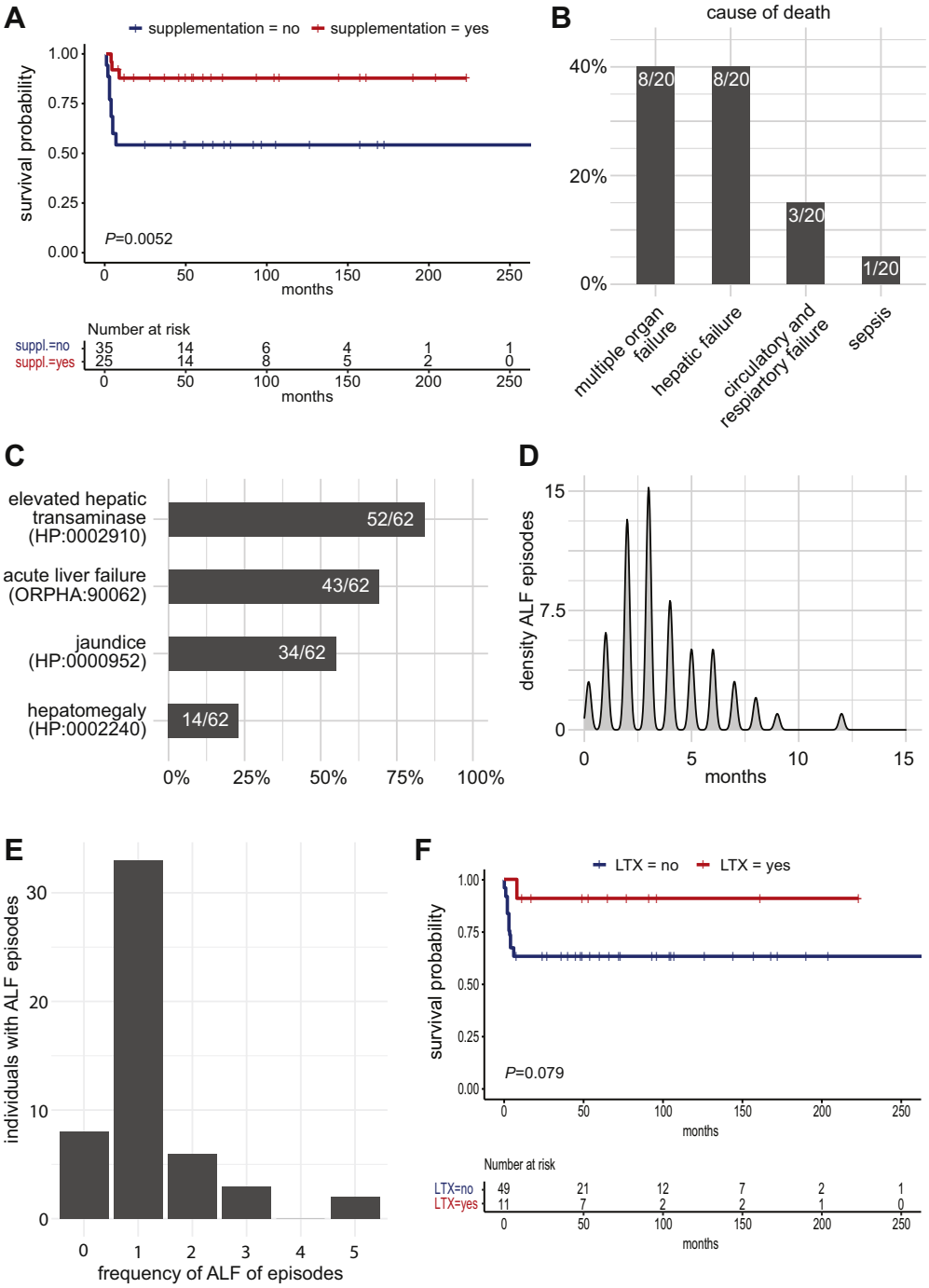

Figure 2 Individual survival and hepatic phenotype. A. Supplementation therapy (red) influences survival probability of individuals with TRMU deficiency as compared with Kaplan-Meier estimates. B. Cause of death for the 14 deceased individuals with TRMU deficiency. C. Most common features of the hepatic 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

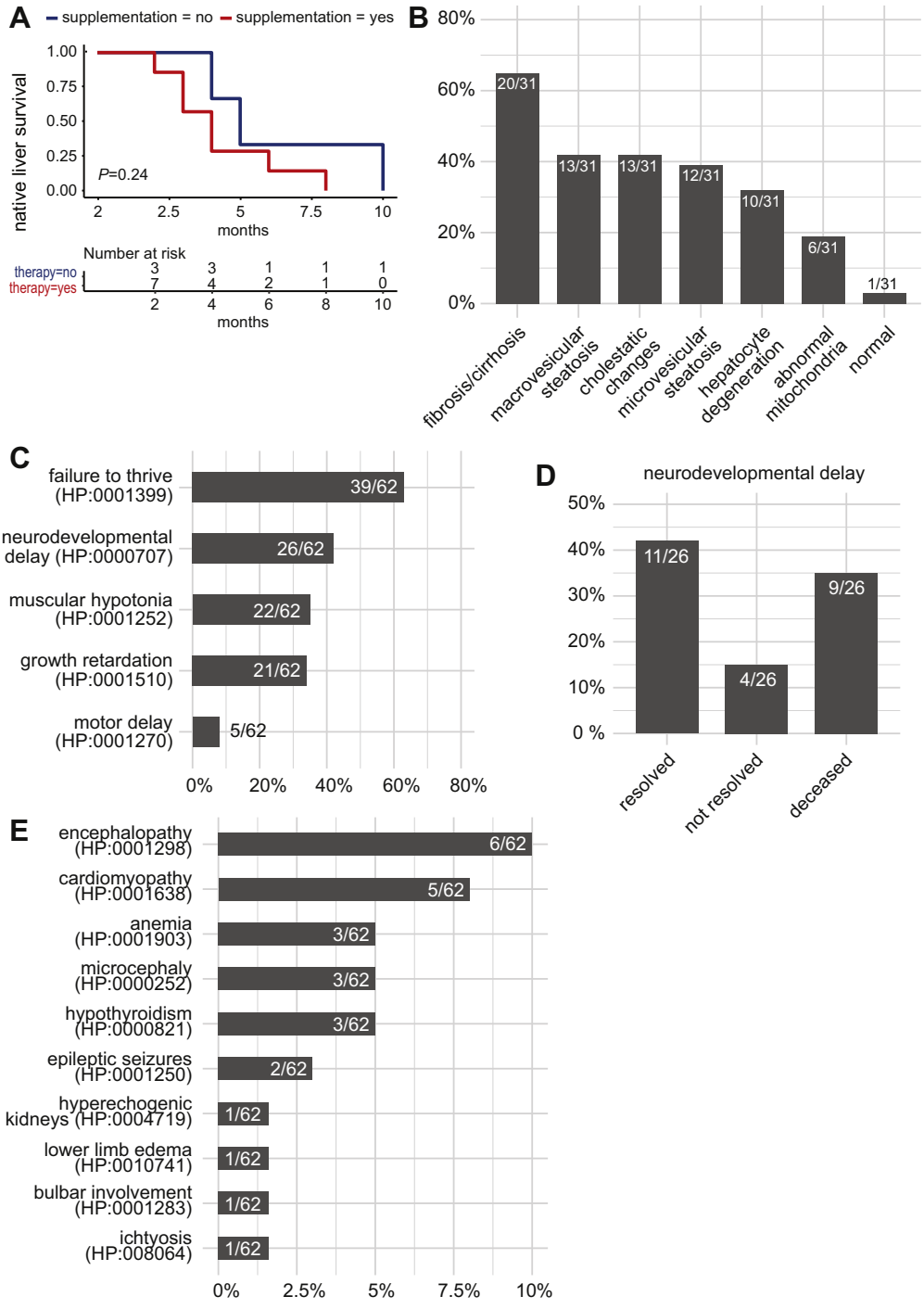

Figure 3 Native liver survival, liver histology, clinical presentation, and course of TRMU-related symptoms. A. Supplementation therapy (blue) does not influence native liver survival, ie, the need for liver transplantation, as compared with Kaplan-Meier estimates. B. Most prevalent findings in liver 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 draw 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.

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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

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