

Additional file 1: Additional Clinical Information

Table 1 MADD-DS3 domains

Group	Rb-unresponsive (severe phenotype; n = 3)			Variably Rb-responsive (moderate phenotype; n = 8)								Rb-responsive (mild phenotype; n = 3)		
Patient	P12	P8	P6	P13	P2	P3	P9	P10	P11	P1	P7	P4	P14	P5
MADD-DS3 domains [1]														
Age at onset	3	3	3	0	0	0	0	0	0	3	0	0	0	0
Congenital anomalies	0	0	6	0	0	0	0	0	0	0	0	0	0	0
Cardiac	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CNS	0	0	0	0	0	0	2.25	0	0	2.25	4.5	0	0	0
PNS	0	0	0	0	0	0	0	0	0	0	0	1.5	0	0
Liver	6	6	6	0	0	3	1.5	6	0	4.5	6	0	4.5	6
Muscle	6	3	6	3	3	3	3	0	3	1.2	3	4	3	2.4
Patient-reported outcome	9	9	9	0	0	0	0	3	6	3	9	0	0	3
Total MADD-DS3 score	24	21	30	3	3	6	6.75	9	9	13.95	22.5	5.5	7.5	11.4

Abbreviations: CNS: central nervous system; MADD-DS3: multiple acyl-CoA dehydrogenase deficiency-disease severity 3; n: number of patients; PNS: peripheral nervous system; Rb: riboflavin.

Table 2 Clinical symptoms applicable to MADD-DS3 domains

Group	Rb-unresponsive (severe phenotype; n = 3)			Variably Rb-responsive (moderate phenotype; n = 8)								Rb-responsive (mild phenotype; n = 3)		
Patient	P12	P8	P6	P13	P2	P3	P9	P10	P11	P1	P7	P4	P14	P5
MADD-DS3 domains [1]														
Congenital anomalies														
<i>Hydronephrosis</i>	U	U	+	–	–	–	–	–	–	–	–	–	–	–
Cardiac														
<i>Patent foramen ovale</i>	U	U	+	–	–	–	–	–	–	–	–	–	–	–
<i>Pulmonary valve stenosis</i>	U	U	+	–	–	–	–	–	–	–	–	–	–	–
CNS														
<i>Epilepsia partialis continua</i> (resolved)	–	–	–	–	–	+	–	–	–	–	–	–	–	–
<i>Delayed gross motor development</i>	–	–	–	–	+	–	–	–	–	–	+	–	–	–
<i>Cerebral white matter abnormality</i>	–	–	–	–	–	–	–	–	–	–	–	–	–	+
<i>Migraine/paroxysmal headache</i>	–	–	–	–	+	–	–	–	–	+	+	–	–	–
<i>Learning disabilities</i>	–	–	–	–	–	–	–	–	–	+	–	–	–	–
<i>Intellectual disabilities</i>	–	–	–	–	–	–	+	–	–	–	–	–	–	–
<i>Encephalopathy</i>	–	–	–	–	–	–	–	–	–	–	–	–	+	–
<i>Seizures</i>	–	–	+	–	–	+	–	–	–	–	+	–	–	–
<i>Drooling</i>	–	–	–	–	–	–	–	–	–	+	–	–	–	–
<i>Stroke</i>	–	–	–	–	–	–	–	–	–	–	+	–	–	–
<i>Coma</i>	–	–	–	–	–	–	–	+	+	–	+	–	–	–
<i>Lethargy</i>	–	–	–	–	+	+	–	–	–	–	–	+	–	–
Liver														
<i>Increased liver enzymes</i>	–	–	+	–	–	–	–	+	–	–	+	–	–	–
<i>Acute hepatic failure</i>	–	–	–	–	–	–	–	–	–	–	+	–	–	+
<i>Hepatic steatosis</i>	–	–	–	–	–	–	–	–	–	+	+	–	–	+
<i>Hepatomegaly</i>	–	–	–	–	+	–	–	+	–	–	+	–	–	–
<i>Hepatosplenomegaly</i>	–	–	–	–	–	–	–	–	–	–	–	–	–	+

Table 2 (cont.)

Group	Rb-unresponsive (severe phenotype; n = 3)			Variably Rb-responsive (moderate phenotype; n = 8)								Rb-responsive (mild phenotype; n = 3)		
Patient	P12	P8	P6	P13	P2	P3	P9	P10	P11	P1	P7	P4	P14	P5
MADD-DS3 domains [1]														
Neuromuscular														
<i>Beevor's sign</i>	–	–	–	+	–	–	–	–	–	–	–	–	–	–
<i>Elevated CK</i>	–	–	–	–	–	–	–	–	+	–	+	+	–	+
<i>Facial weakness</i>	–	–	–	+	–	–	–	–	–	–	–	–	–	–
<i>Neck muscle weakness</i>	–	–	–	+	+	+	–	–	+	–	+	–	+	+
<i>Susceptibility to fatigue</i>	–	–	–	–	+	+	–	–	–	–	–	–	–	–
<i>DM weakness lower limbs</i>	–	–	–	+	+	–	–	–	–	–	–	–	–	–
<i>DM weakness upper limbs</i>	–	–	–	–	+	–	–	–	–	–	–	+	–	–
<i>PM weakness upper limbs</i>	–	–	–	+	+	–	–	–	–	–	–	+	+	–
<i>PM weakness lower limbs</i>	–	–	–	+	+	–	–	–	–	–	–	+	+	–
<i>Weakness</i>	–	–	–	–	+	–	–	–	–	–	+	+	–	+
<i>Hypotonia</i>	–	+	–	–	+	+	+	–	–	+	+	–	–	–
<i>Myopathy</i>	–	–	–	–	+	–	–	–	–	+	+	+	–	+
<i>Pain/myalgia</i>	–	–	–	–	–	+	–	+	–	+	–	–	–	–

Abbreviations: +: reported; CK: creatine kinase; CNS: central nervous system; DM: distal muscle; MADD-DS3: multiple acyl-CoA

dehydrogenase deficiency-disease severity 3; n: number of patients; PM: proximal muscle; Rb: riboflavin; U: unknown.

Table 3 Additional clinical symptoms

Group		Rb-unresponsive (severe phenotype; n = 3)			Variably Rb-responsive (moderate phenotype; n = 8)								Rb-responsive (mild phenotype; n = 3)		
Patient		P12	P8	P6	P13	P2	P3	P9	P10	P11	P1	P7	P4	P14	P5
Metabolic															
	<i>Hyperammonaemia</i>	+	+	+	–	–	–	–	–	–	–	+	–	+	+
	<i>Metabolic acidosis</i>	+	+	+	–	–	–	+	–	–	+	–	–	–	–
	<i>Aminoaciduria</i>	–	–	+	–	–	–	–	–	–	–	–	–	–	–
	<i>Hypoglycaemia</i>	+	–	+	–	–	–	–	+	+	+	+	–	+	+
	<i>Lactic acidosis</i>	–	–	+	–	–	–	–	–	–	–	–	–	–	–
	<i>Ketosis</i>	–	–	–	–	+	+	+	+	–	–	+	–	+	+
Gastrointestinal															
	<i>Chronic constipation</i>	–	–	–	–	–	–	–	+	–	+	–	–	–	–
	<i>Abdominal pain</i>	–	–	–	–	+	+	–	–	–	–	–	–	–	–
	<i>Diarrhoea</i>	–	–	–	–	–	–	+	–	–	–	–	–	–	–
	<i>Vomiting</i>	–	+	–	–	+	+	–	–	+	–	–	–	+	–
Kidney															
	<i>Acute kidney injury</i>	+	–	–	–	–	–	–	–	–	–	–	–	–	–
Skeletal															
	<i>Lumbar hyperlordosis</i>	–	–	–	+	–	–	–	–	–	–	–	–	–	–
	<i>Scapular winging</i>	–	–	–	+	–	–	–	–	–	–	–	–	–	–
	<i>Osteopaenia</i>	–	–	–	–	–	–	–	–	–	+	–	–	–	–
Other															
	<i>Intra-uterine growth restriction</i>	–	–	+	–	–	–	–	–	–	–	–	–	–	–
	<i>Restrictive ventilatory defect</i>	–	–	–	+	–	–	–	–	–	–	–	–	–	–
	<i>Obstructive sleep apnoea</i>	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	<i>Recurrent infections</i>	–	–	–	–	–	–	–	+	+	–	–	–	–	–
	<i>New-onset pancytopenia</i>	+	–	+	–	–	–	–	–	–	–	–	–	–	–
	<i>Astigmatism</i>	–	–	–	–	–	–	–	+	–	–	–	–	–	–

Abbreviations: +: reported; n: number of patients; Rb: riboflavin.

References:

- [1] van Rijt WJ, Ferdinandusse S, Giannopoulos P, Ruiters JPN, de Boer L, Bosch AM, *et al.* Prediction of disease severity in multiple acyl-CoA dehydrogenase deficiency: a retrospective and laboratory cohort study. *J Inherit Metab Dis.* 2019;42:878–89.