Supplementary Material

Complex I deficiency: clinical features, biochemistry and molecular genetics

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Supplementary Table 1

Gene (Complex I subunits)	Number of patients	Age at Onset	Age at Death	Clinical phenotype	Lactate (normal <2.0 mM)	Complex I deficiency (% residual actvity compared to mean control)	Gene change(s)	Protein change(s)	References
NDUFV1	2	5 months	14 and 17 months	myoclonic epilepsy	CSF elevated	M and Fb low	cpd het c.175C>T + c.1268C>T	R59X + T423M	Schuelke M et al. Nat Genet. 1999 Mar [1]
	1	6 months	10 years	(macrocystic) leuko-encephalopathy	CSF elevated	M and Fb low	homozygous c.1022 C>T	A341V	
	1	1 year	3 years	LS*	B 2.6 mM	M low (Fb normal)	cpd het c.640G>A + A>C intron 8 splice site	E214K + exon 8 skipping -> unstable mRNA	Bénit P et al. Am J Hum Genet. 2001 Jun [2]
	1	6 months	18 months	LS	B 4 mM	M low (Fb normal)	cpd het c.1294G>C + c.989–990del2	A432P + premature stop codon -> unstable mRNA	
	1	5 months	alive at 3 years	LS	B 4.7 mM	M low (Fb normal)	cpd het c.611A>G + c.616T>G	Y204C + C206G	
	1	First months	not reported	leukodystrophy	CSF elevated	M 36% (Fb normal)	homozygous c.1022C>T	A341V	Bugiani M et al Biochim Biophys Acta. 2004 Dec [3]
	1	7 months	alive at 7 years	LS	B 3.7- 8.0 mM; CSF 4.8 mM	M 32%‡ (Fb normal)	cpd het c.611A>G + c.616T>G	Y204C + C206G	Laugel V et al Pediatr Neurol. 2007 Jan [4]
	1	9 months	alive at 16 months	(cystic) leuko-encephalopathy	B 1.8 mM	M 30%‡; Fb 31%‡	cpd het c.770G>A + c.632T>C	R257Q + A211V	Zafeiriou DI et al. Neuropediatrics. 2008 Jun [5]
	2	6 and 11 months	alive at 32 months	leuko-encephalopathy	CSF 55 + 44 mg/dL (normal ≤ 20)	M 38%	homozygous c.1156C>T	R386C	Breningstall GN et al. Semin Pediatr Neurol. 2008 Dec [6]
	1	2 weeks	4 months	FILA	B 21.6 mM; CSF 18.1 mM	M 11%; Fb 20%	homozygous c.1129G>A	E377K	Calvo SE et al. Nat Genet. 2010 Oct [7]
	2	3.5 months	4.5 months	LS	B 1.7 + 5.2 mM; CSF 2.3 + 2.8 mM	M low (liver normal)	homozygous c.1156G>A	R386H	Vilain C et al. Clin Genet. 2011 Jun [8]
NDUFV2	3	5 days	3 months	HCM	B persistently >5 mM	M 40-50%	homozygous 4bp deletion of intron 2 IVS2+5+8delGTTA	skipping of exon 2	Bénit P et al Hum Mutat. 2003 Jun [9]

NDUFV2	1	not reported	not reported	HCM	not reported	F 15%‡	homozygous 4bp deletion of intron 2 IVS2+5+8delGTTA	skipping of exon 2	Pagniez-Mammeri H et al. Mol Genet Metab. 2009 Apr [10]
NDUFA1	2	4 and 9 months	14 months	LS	B 32 mg/dl (normal <20)	M 20%‡; Fb 17%‡	hemizygous c.22G>C	G8R	Fernandez-Moreira D et al Ann Neurol. 2007 Jan [11]
	1	6 months	alive at 10 years	cerebellar ataxia and myoclonic epilepsy	B normal	M 30%‡; Fb 70%‡	hemizygous c.251G>C	R37S	
	1	4 years	alive at 35 years	cerebellar ataxia and neuro-degeneration	B and CSF normal	M 5–10%	hemizygous c.94G>C	G32R	Potluri P et al Mol Genet Metab. 2009 Apr [12]
	1	5 years	alive at 30 years	cerebellar ataxia and neuro-degeneration	B 3 mM: CSF 2 mM	M 5–10%	hemizygous c.94G>C	G32R	
	1	11 months	alive at 5 years	lactic acidosis (recurrent episodes)	B 3–4 mM	M 20%	hemizygous c.94G>C	G32R	Mayr A et al. Mol Genet Metab. 2011 May [13]
NDUFA2	1	5 days	11 months	HCM and LS	not reported	M 20%‡; Fb 36%‡	homozygous c.208+5G >A	impaired exon 2 splicing -> frameshift -> unstable truncated protein -> degraded	Hoefs SJ et al Am J Hum Genet. 2008 Jun [14]
NDUFA9	1	soon after birth	1 month	LS	B 10 mM	M 29%; F 11%	homozygous c.962G>C	R321P	van den Bosch BJ et al J Med Genet. 2011 Nov [15]
NDUFA10	1	<10 months	23 months	LS* and HCM	B 8.6 mM; CSF 4.9 mM	M 19%; Fb 3% (and Fb CIII 34%)	cpd het c.1A>G + c.425A>G	M1? + Q142R	Hoefs SJ et al. Eur J Hum Genet. 2011 Mar [16]
	1	>6 months	progressive course	LS	B and CSF elevated	M <25%; Fb <25%	homozygous c.296G>A	G99E	Haack TB et al. J Med Genet. 2012 Feb [17]
NDUFA11	3	10 to 24 hours	40 days	FILA and HCM	B 10–15 mM	M 4--27%; Fb 45%	homozygous IVS1+5 G>A	leaky splicing -> activation of cryptic splice site at 19-20bp of exon 1, lacking the 3' 78bp of exon 1	Berger I et al Ann Neurol. 2008 Mar [18]
	3	3 to 4 months	18 months ; 4 years; one patient alive at 6 months	HCM and encephalopathy	B 3.2–10 mM	M 19-39%; Fb 46%	homozygous IVS1+5 G>A		
NDUFA12	1	2 years	alive at 10 years	LS	B 4.9 mM; CSF 2.9 mM	M 11%; Fb 60%	homozygous c.178C>T	R60X	Ostergaard E et al. J Med Genet. 2011 Nov [19]
NDUFB3	1	intra-uterine	4 months	FILA	B 5.1 mM	M 6% (M CII+III 17% + CIV 54% - ?PM artefact); Fb 12% (Fb CIII 50%)	homozygous c.64T>C	W22R	Calvo SE et al. Sci Transl Med. 2012 Jan [20]

NDUFB3	1	not reported	not reported	unspecified encephalo-myopathy	B elevated	Fb 17%	cpd het c.64T>C + c.208G>T	W22R + G70X	Haack TB et al. J Med Genet. 2012 April [17]
NDUFB9	1	<6 months	progressive course	unspecified encephalo-myopathy	B elevated	M >50%‡; Fb 21-39%‡	homozygous c.191T>C	L64P	Haack TB et al. J Med Genet. 2012 Feb [21]
NDUFS1	3	2 years; 4 months	10 months; 7 months	leukodystrophy	B 4.4 mM; CSF 3.2 mM	M and Fb low	cpd het 3bp deletion at c.664-6 + c.755 A>G	in-frame codon 222 deletion + D252G	Bénit P et al. Am J Hum Genet. 2001 Jun [2]
	2	2 and 3 months	5 months; 3 months	LS	B and CSF persistently high (5 mM)	M and Fb low	cpd het c.721 C>T + c.1669 C>T	R241W + R557X -> unstable mRNA	
	1	shortly aFbter birth	not reported	LS	B 5.3 mM; CSF 4 mM	M (Fb normal)	cpd het 2119 A>G + de novo deletion of paternal *NDUFS1* allele	hemizygous M707V; de novo deletion of paternal NDUFS1 allele	
	2	6 months	not reported	leukodystrophy	B elevated	M 45%; Fb 45%	homozygous c.1564C>A	Q522K	Bugiani M et al Biochim Biophys Acta. 2004 Dec [3]
	1	8.5 months	14 months; 8 months	LS	B 24 mg/dL (normal < 20); CSF 30 mg/dL (normal < 15)	M 25%	homozygous c.691C>G	L231V	Martín MA et al. Arch Neurol. 2005 Apr [22]
	1	<6 months	not reported	leuko-encephalopathy	B 1.9 mM; CSF 6.6 mM	Fb 27%	cpd het c.683T>C + c.755A>G	V228A + D252G	Pagniez-Mammeri H et al. Mol Genet Metab. 2009 Apr [10]
	1	8 months	12 years	(cystic) leukodystrophy	not reported	M 63%‡; Fb 27%‡	cpd het c.1669C>T + c.1855G>A	R557X + D619N	Hoefs SJ et al Mol Genet Metab. 2010 Jul [23]
	2	4 months	8 months; 7 months	leuko-encephalopathy	B and CSF elevated	M 10%‡ (M CIII 70%‡); Fb 20%‡	homozygous c.1222C>T	R408C	
	1	5 months	2 years	unspecified encephalo-myopathy	not reported	Fb 24%‡	cpd het c.631–633del-GAA + c.683T>C	211delE + V28A	
	2	4 and 2 months	10.5 months; 10 months	LL	B 3.3 mM; CSF 4.7 mM	M 23%	homozygous c.1222C>T	R408C	Tuppen HA et al Brain. 2010 Oct [24]
	2	11 months	not reported	(macrocystic) leuko-encephalopathy	B 2.4 + 5.1 mM (2.86 mM in CSF)	M 45% + 98%‡; Fb 146% + 53%	homozygous c.1783A>G	T595A	Ferreira M et al. Neurogenetics 2011 Feb [25]
	1	5 months	3 years 10 months	leukodystrophy	B persistently elevated	Fb ~40%‡	cpd het c.497G>A + c.683T>C	G166E + V228A	Danhauser et al. Mol Genet Metab 2011 Jun [26]
	1	6 months	1 year 7 months	leukodystrophy	B persistently elevated	not reported	cpd het c.683T>C + c.755A>G	V228A + D252G	
	1	<6 months	progressive course	unspecified encephalo-myopathy	B and CSF elevated	M <50%; Fb <50%	cpd het c.212T>A + c.384T>A	V71D + C128X	Haack TB et al. J Med Genet. 2012 Feb [21]

NDUFS1	1	<6 months	progressive course	leukodystrophy	B and CSF elevated	M <50%; Fb <50%	cpd het c.1912insA + c.208A>G	T638NfsX14 + Y695C	
	1	>6 months	progressive course	leukodystrophy	B elevated	M <50%; Fb <50%	cpd het c.2083T>C + c.2084A>G	Y695H + Y695C	
	1	>6 months	not reported	(macrocystic) leuko-encephalopathy	not reported	M 14.5%; Fb 50%	cpd het c.1669C>T + c.1783A>G	R557X + T595A	Invernizzi F et al. Mitochondrion 2012 Mar [27]
NDUFS2	2	6 months	24 months	HCM and encephalopathy	B 9.9 + 12 mM; CSF 7.8 mM	M 20%; Fb 22-31%	homozygous c.683G>A	R228Q	Loeffen J et al Ann Neurol. 2001 Feb [28]
	1	day 1	4 days	HCM	B 24 mM	M 8.4%; Fb 20.5%	homozygous c.686C>A	P229Q	
	3	7 and 10 months	18 months; 3 years; 2 years	LS	B 4.2, 5.0 + 12.5 mM; CSF 3.3 mM	M 24%; Fb 23%	homozygous c.1237T>C	S413P	
	1	2 hours	3.5 months	FILA	B 18 mM	M 16%	cpd het c.413G>A + c.998G>A	R138Q + R333Q	Tuppen HA et al Brain. 2010 Oct [24]
	1	8 months	22 months	LS	B 11.7 mM; CSF 5.6 mM	M 20%	cpd het c.353G>A + c.875T>C	R118Q + M292T	
	1	soon after birth	alive at 9 years	LL	not reported	M 27%	cpd het c.875T>C + c.1328T>A	M292T + M443K	
	1	infancy	alive at 11 years	LL	B and CSF normal	M 13%	cpd het c.442G>A + c.875T>C	E148K + M292T	
	1	34 months	alive at 6 years	LL	B 3.2 mM; CSF 2.7 mM	not reported	cpd het c.866+4A>G + c.875T>C	splicing abnormality + M292T	
	1	<6 months	progressive course	HCM	B and CSF elevated	M <25%; Fb <25%	cpd het c.329A>T + c.968G>A	D110V + R323Q	Haack TB et al. J Med Genet. 2012 Feb [21]
NDUFS3	1	9 months	13.5 years	LS	CSF 2.7 mM	M 21%; Fb 76%‡	cpd het c.434C>T + c.595C>T	T145I + R199W	Bénit P et al. J Med Genet. 2004 Jan [29]
	1	not reported	not reported	unspecified encephalo-myopathy	B elevated	M 28%; Fb 36%	homozygous c.532C>T	R199W	Haack TB et al. J Med Genet. 2012 April [17]
NDUFS4	1	8 months	16 months	LL	B and CSF normal	M 43%‡ (M CIII 75%‡)	homozygous 5-bp duplication c.466_470dupl AAGTC	frameshift resulting in K158fsX31	van den Heuvel L et al Am J Hum Genet. 1998 Feb [30]
	1	1 week	3 months	LS	B 5.5 mM; CSF 7.6 mM	M 22.4%‡; Fb 47%‡ (Fb CIII 87%‡)	homozygous c.289delG	W96X	Budde SM et al Biochem Biophys Res Commun. 2000 Aug [31]
	1	7 weeks	3 months	LS and HCM	B 3.0 mM; CSF 3.4 mM	M 14%‡ (M CIII 57%‡); Fb 60%‡ (Fb CIII 67%)	homozygous c.C316T	R106X	
	1	4 months	8 months	LS	B 2.4-3.9 mM; CSF 3.4 mM	M 10% (M CIII 91%); Fb 30% (Fb CIII 88%)	homozygous c.C316T	R106X	Budde SM et al J Inherit Metab Dis 2003 Mar [32]
	1	4	not	LS	not reported	not	homozygous	D60fs	Lebre AS et al. J

		months	reported			reported			
	1	>6 months	not reported	LS	not reported	not reported	cpd het	W97fs + S159fs	Med Genet. 2011 Jan [33]
	1	2 weeks	7 months	LL and HCM	B elevated	M 35%; Fb 16%	homozygous c.44G>A	W15X	Petruzzella V et al Hum Mol Genet. 2001 Mar [34]
	2	2 months	4 months	LS	B 6–7 mM; CSF 3.9 mM	M 80%‡	homozygous IVS1nt-1, G>A	skipping of exon 2	Bénit P et al Hum Genet. 2003 May [35]
	1	4 months	6 months	LS and HCM	B and CSF elevated	M 4% (M CIII 107%); Fb 34% (Fb CIII 87%)	homozygous c.178_528del; Exon 3-5 deletion	D60_K175del; no protein product?	Rötig et al., Biochim Biophys Acta 2004 [36]; Assouline Z et al. Biochim Biophys Acta. 2012 Feb [37]
	3	3.5 months	10 months	LS and HCM in one case; LS in twp	B 1.0 -9.5 mM; CSF 4.5 mM	M low	homozygous c.462delA	N154fsX33	Anderson SL et al J Inherit Metab Dis. 2008 Dec [38]
NDUFS4	1	8 months	2.4 years	LS	not reported	M 54%	cpd het c.115G>A + c.462delA	N119H + K154fs	Leshinsky-Silver E et al. Mol Genet Metab. 2009 Jul [39]
	1	3 months	not reported	LS	B 3.1 mM; CSF3.6 mM	M 8% (M CIV 38%); Liver 9% (Liver CIV 54%); Fb 16%	cpd het c.99-1G>A + c.462delA	S34IfsX4 (skipping of exon 2) + K154NfsX35	Calvo SE et al. Nat Genet. 2010 Oct [7]
	1	4 months	2 weeks	LS	B 4.4 mM; CSF 3.9 mM	M 3% (M CIV 66%); Fb 15%	cpd het c.99-1G>A + c.351-2A>G	S34IfsX4 (exon 2 skipping); transcript unstable	
	1	5 days	not reported	encephalopathy	B elevated	M 6%; Fb 47%	homozygous c.99-1G>A	S34IfsX4 (exon 2 skipping)	Assouline Z et al. Biochim Biophys Acta. 2012 Feb [37]
	1	3 months	6 months	LL and HCM	B and CSF elevated	M 35%; Fb 69%	homozygous c.291delG	W97X	
	1	22 months	24 months	LL	not reported	M 33%; Fb 76%	cpd het c.472dupAAGTC	Y160SfsX31	
	1	3 months	4.5 months	LS	B and CSF elevated	M low	homozygous c.99-1G>A	S34IfsX5 (skipping of exon 2)	
	1	<6 months	progressive course	LS and HCM	B and CSF elevated	M <50%	homozygous c.316C>T	R106X	Haack TB et al. J Med Genet. 2012 Feb [21]
NDUFS6	1	shortly after birth	6 days	FILA	B 6-12 mM	Fb 7%‡	homozygous 4.175-kb deletion encompassing exons 3 and 4	no protein product	Kirby DM et al J Clin Invest. 2004 Sep [40]

NDUFS6	2	shortly after birth	11 days	FILA	B 6.5 mM	Fb 4%‡	homozygous c.186+2T>A	frameshift -> premature stop codon predicting truncated protein of 71 instead of 124 amino acids	
	2	day 2	8 days	FILA	B 6.0-11.2 mM; CSF 8.1 mM	M 45%‡	homozygous c.344G>A	C115Y	Spiegel R et al Eur J Hum Genet. 2009 Sep [41]
	2	6 days	8 days	FILA	B 16.8 mM; CSF 18.4 mM	M 56%	homozygous c.344G>A	C115Y	
	1	<6 months	progressive course	unspecified encephalo-myopathy	B elevated	M <50%; Fb <50%	homozygous c.352C>T	Q118X	Haack TB et al. J Med Genet. 2012 Feb [21]
NDUFS7	2	8 and 11 months	3 years 11 months; 5 years	LS* ; LS	B and CSF normal	M 23 + 28%‡	homozygous c.364G>A	V122M	Triepels RH et al Ann Neurol. 1999 Jun [42]
	1	15 months	not reported	LS	B 4.8 mM; CSF 2.8 mM	Fb 62%‡	homozygous c.434G>A	R145H	Lebon S et al. Mol Genet Metab. 2007 Apr [43]
	2	4 months	5 months; 6 months	LS x2	B 15 mM	M 38%; Fb 68%	Homozygous insertion of 122bp cryptic exon (corresponding to first intron of *NDUFS7*) between exons 1 and 2; C>G substitution five nucleotides after 122bp insertion (c.17-1167 C > G)	frameshift -> shortened protein	Lebon S et al. Mol Genet Metab. 2007 Sep-Oct [44]
NDUFS8	1	day 1	11 weeks	LS* and HCM	B 3.4 mM; CSF 5.6 mM	M 39%‡; Fb 69%	cpd het c.236C>T + c.305 G>A	P79L + R102H	Loeffen J et al. Am J Hum Genet. 1998 Dec [45]
	1	7 years	alive at 9y	LS	B and CSF normal	M 31%	cpd het c.254C>T + c.413 G>A	P85L + R138H	Procaccio V et al. Neurology. 2004 May [46]
	1	4 weeks	3 months	FILA	B 7.4 mM; CSF 5.5 mM	M 30%	homozygous c.236C>T	P79L	Tuppen HA et al Brain. 2010 Oct [24]
	1	8 months	14 months	leukodystrophy	B 3.0 mM: CSF 2.3 mM	M 8% (+ 52% residual CIV)	homozygous c.460G>A	G154S	Calvo SE et al. Nat Genet. 2010 Oct [7]
	1	not reported	not reported	HCM and encephalopathy	not reported	M 38%; Fb 52%	cpd het c.229C>T + c.476C>A	R77W + A159D	Haack TB et al. J Med Genet. 2012 April [17]
	2	not reported	not reported	LS x2	B elevated	M 8%; Fb 54%	homozygous c.187G>C	E63Q	

Gene (Complex I assembly factors)	Number of patients	Age at Onset	Age at Death	Clinical phenotype	Blood lactate (normal <2.0 mM)	CI def in muscles related to ctr mean	Gene change(s)	Protein change(s)	References
NDUFAF1; CIA30	1	11 months	alive at 20y	HCM and later multisystem disease	B 5–10 mM in first few years of life; later 2.5–3.5 mM	Fb 36%	cpd het c.1001A>C + c.1140A>G	T207P + K253R	Dunning CJ et al. EMBO J. 2007 Jul [47]
	1	6 months	6.5 months	HCM	B 9-18 mM	M 25%; Fb 60%	cpd het c.631C>T + c.733G>A;	R211C + G245R	Fassone E et al. J Med Genet. 2011 Oct [48]
NDUFAF2; NDUFA12L; B17.2L; Mimitin	1	12 months	13 years 7 months	LL	B normal; CSF 4.2 mM	M 38%; Fb <20%	hemizygous c.182C>T	R45X	Ogilvie I et al. J Clin Invest. 2005 Oct [49]
	1	20 months	2 years	LL	B and CSF repeatedly normal	M 36%	homozygous c.1A>T	M1L	Barghuti F et al. Mol Genet Metab. 2008 May [50]
	1	8 months	18 months	LS	B normal; CSF 2.6 mM	M 24% (53% in fb)	homozygous c.1A>T	M1L	
	1	3 months	1 year	LS	B 3-5 mM	Fb 21%‡	homozygous c.114C>G	Y38X	Hoefs SJ et al. Hum Mutat. 2009 Jul [51]
	1	intra-uterine	14 months	LL	B 2.5–3.4 mM	Fb 45%‡	homozygous ~450kb deletion on chromosome 5, encompassing 3 genes: *ELOVL7*, *ERCC8* and *NDUFAF2*	no protein product	Janssen RJ et al. Hum Mol Genet. 2009 Sep 15 [52]
	1	soon after birth	27 months	LS*	B initially 4.2 mM, subsequently normal; CSF normal	M 12%‡; Fb 40%	homozygous c.9G >A	W3X	Herzer M et al. Neuropediatrics. 2010 Feb [53]
	2	6 and 3 months	17 months; 14 months	LS*; LS	CSF 3.2 mM	Fb 26%	homozygous c.103delA	I35SfsX17	Calvo SE et al. Nat Genet. 2010 Oct [7]
	1	4 months	15 months	LS	CSF 2.4 mM	Fb 32%	homozygous c.221G>A	W74X	
NDUFAF3; C3ORF60	3	1 to 3 days	3 months	FILA x3	B persistently markedly elevated (peak 27 mM)	M 32-40%; Fb 39%	homozygous c.229 G>C	G77R	Saada A et al. Am J Hum Genet. 2009 Jun [54]
	1	3 weeks	4 months	FILA	B 5.4 mM; CSF 6 mM	M 26%; Fb 18%	homozygous c.365 G>C	R122P	
	1	3 months	6 months	encephalopathy including myoclonic epilepsy	B peak 27 mM	M nd; Fb 33%	cpd het c.2T>C + c.365G>C	M1T + R122P	

NDUFAF4; C6ORF66; HRPAP20	9	soon after birth	3 died at 2–5 days; oldest survivor was 7 years at time of report	FILA x3; encephalopathy in other cases	B 38 mM	M 5.5-17%; Fb 32%-67%	homozygous c.194T>C	L65P	Saada A et al. Am J Hum Genet. 2008 Jan [55]
	1	<6 months	progressive course	leukodystrophy	B and CSF elevated	M <25%; Fb <25%	homozygous c.23G>A	G8D	Haack TB et al. J Med Genet. 2012 Feb [21]
C8ORF38	2	7 and 10 months	34 months; alive at 22 months	LS x2	B persistently elevated	M 36%; Fb 14%	homozygous c.296A>G	Q99R; possible splicing defect (at 3′ end of exon 2)	Pagliarini DJ et al. Cell. 2008 Jul [56]; McKenzie M et al. J Mol Biol 2011 Dec [57]
C20ORF7	1	intra-uterine	7 days	FILA	B 3.1-16.5 mM; CSF 20.1 mM	M 10-20%; Fb 5<25%	homozygous c.719T>C	L229P	Sugiana C et al. Am J Hum Genet. 2008 Oct [58]
	3	3 years	36 years; two alive at 23 and 29 years	LS x3	CSF 5 mM	M 36-48%; Fb 6<33%	homozygous c.477A>C	L159F	Gerards M et al. J Med Genet. 2010 Aug [59]
	5	1 year	5.9 years; four cases alive at 2.5, 4.5, 6 and 7 years	LS x5	B 3.0-3.6 mM; CSF 2.7 mM	M ~20% (+ ~35% residual CIV)	homozygous c.749G>T	G250V	Saada A et al. J Inherit Metab Dis. 2012 Jan [60]
FOXRED1	1	day 1	alive at 22 years	LS	B 4-15 mM; CSF 3.2 mM	M 9% (+ 76% residual CIV); Fb 9% (+ 34% residual CII + 31% residual CIII)	cpd het c.694C>T + c.1289A>G	Q232X + N430S	Calvo SE et al. Nat Genet. 2010 Oct [7]
	1	soon after birth	alive at 10 years	unspecified encephalo-myopathy	B 6.8 mM; CSF 4.3 mM	M 7%; Fb 70%	homozygous c.1054C>T	R352W	Fassone E et al. Hum Mol Genet. 2010 Dec [61]
	1	<6 months	progressive course	unspecified encephalo-myopathy	B normal	M <25%; Fb <25%	cpd het c.406C>T + c.615insAGTG	R316W + A206SfsX15	Haack TB et al. J Med Genet. 2012 Feb [21]
NUBPL; hIND1	1	2 years	alive at 8y	leukodystrophy	B normal; CSF 5.2 + 2.7 mM	M 37%; Fb 19%	cpd het c.166G>A + c.815-27T>C on one allele and a deletion that spans exons 1–4 on the other allele	G56R + exon 10 skipping	Calvo SE et al. Nat Genet. 2010 Oct [7]
ACAD9	1	1 month	alive at 18 years	HCM and exercise intolerance	B 3.1-7.6 mM; CSF 3.6 mM	M 31%‡; Fb 30%	homozygous c.1553 G>A	R518H	Nouws J et al. Cell Metab. 2010 Sep [62]
	1	4 months	6 months	HCM and encephalopathy	not reported	M 34%; Fb 32%	cpd het c.187G>T + c.1237G>A	stop codon after 62 amino acids + E413K	

ACAD9	2	24 hours	46 days; alive at 5 years	HCM and encephalopathy; HCM and exercise intolerance	B 4 mM	M 39% (+ slightly reduced CV); Fb 9% (52% CV)	cpd het c.130T>A + c.797G>A	F44I + R266Q	Haack TB et al. Nat Genet. 2010 Dec [63]; Haack TB et al. J Med Genet. 2012 Feb [21]
	1	<6 months	12 years	HCM and encephalopathy	B elevated	Fb 13%	cpd het c.797G>A + c.1249C>T (identical to a mutation in the homologous region of ACADVL)	R266Q + R417C	
	1	<6 months	2 years	HCM and encephalopathy	B elevated	Fb 26%	cpd het c.976G>C (found in 3% of controls) + c.1594C>T	A326P + R532W	
	3	>4 years	alive at 15, 22 and 24 years	exercise intolerance	B 2.7-6.5 mM	M low; Fb 38-50%	homozygous c.1594C>T	R532W	Gerards M et al. Brain. 2011 Jan [64]; Scholte HR et al. Biochim Biophys Acta. 1995 May [65]
	1	not reported	not reported	exercise intolerance	B 7.8 mM	M low	cpd het c.380G4A (*in cis* + c.379A4C) + c.1405C4T	R127Q + R469W	
	1	<1 month	not reported	HCM	B elevated	Fb low	cpd het c.260T>A + c.976G>C	I87N + A326P	Calvo SE et al. Sci Transl Med. 2012 Jan [20]
	3	not reported	not reported	exercise intolerance	B elevated	M 3%	homozygous c.1594C>T	R532W	Haack TB et al. J Med Genet. 2012 April [17]

Key: ‡ = % of lowest control; B = blood; cpd het = compound heterozygous; CSF = cerebrospinal fluid; Fb = fibroblast; FILA = fatal infantile lactic acidosis; LL = Leigh-like syndrome; LS = Leigh syndrome; LS* = neuropathologically proven LS; M = muscle; nd = not determined; PM = post mortem

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