SUPPLEMENTARY INFORMATION

The Spectrum of Mitochondrial Ultrastructural Defects in Mitochondrial Myopathy

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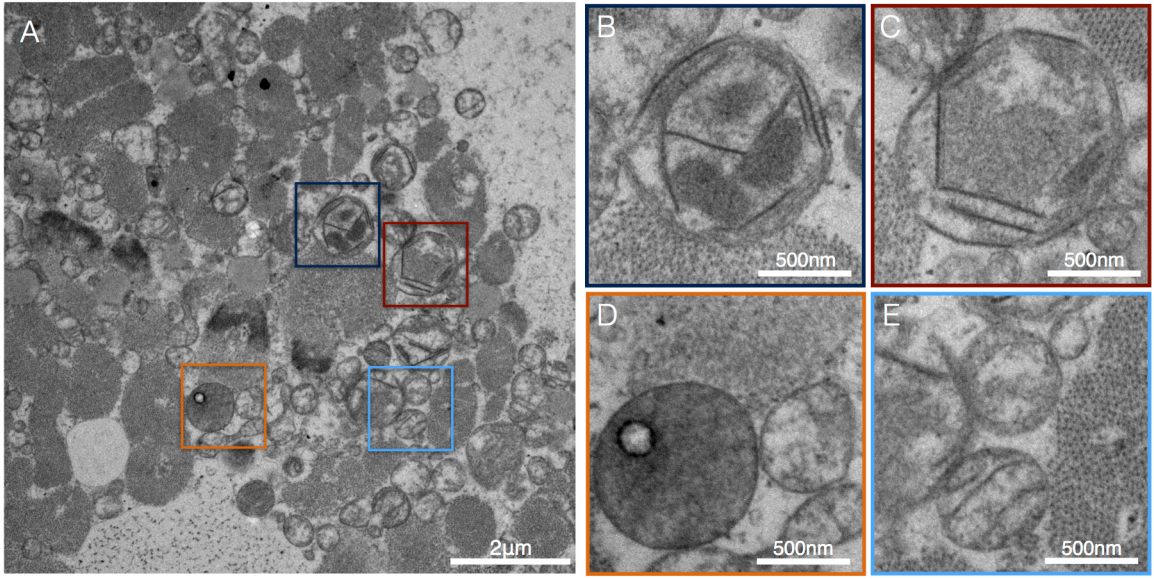

Figure S1. **Mitochondrial morphology and ultrastructure is heterogenous within muscle fibers. (A)** Low magnification electron micrograph of muscle fiber region containing mitochondria exhibiting different ultrastructural defects in patient 4 (m. 8344A>G). **(B-E)** Higher magnification images of selected areas in (A) showing heterogeneity in mitochondrial sizes, electron density, inclusion types, and cristae appearance and organization.

Supplementary Table 1: Results from a systematic review of literature of electron microscopy studies (n = 135) in skeletal muscle of patients with confirmed mitochondrial myopathy.

Author (Year)	Muscle	Age*	Clinical	Genetics	Ultrastructural abnormality
van Wijngaarden *et al.* (1967)	Deltoid and gastrocnemius	15 years	[Pediatric] Myopathy without muscle atrophy, deltoid muscle weakened, paresis of pelvic muscles (n=1).	N.S.	Matrix swelling and electron lucent mitochondria; clumped and filamentous, small osmiophilic dense bodies present in mitochondrial matrix; larger electron-dense round granules or irregularly shaped inclusions of moderately electron dense granular material.
Afifi *et al.* (1972)	N.S.	19 years	Hypermetabolic "mitochondrial" disease. Substantial muscle weakness (n=1).	N.S.	Osmiophilic inclusions of variable size and density within mitochondria; dense inclusions replacing most of the cristae, with cristae reduced to a thin circular rim at the periphery of affected mitochondria.
Hudgson *et al.* (1972)	Peroneus longus and biceps	35 years (proband) and 12 years (niece).	Familial "mitochondrial" myopathy. Facial and ocular, pectoralis major and bicep weakness, considerable lower limb weakness (n=2).	Dominant inheritance; high penetrance; maternal transmission. Mutation N.S.	Giant mitochondria measuring up to 3 μm containing concentric cristae and small electron-dense inclusions; mitochondria with "parking-lot" type inclusions between inner and outer mitochondrial membranes; mitochondrial with six layers with periodicity between both their transverse and axial cristae of approximately 75 A.
Adachi *et al.* (1973)	Ocular muscles	37 years	CPEO, cerebella ataxia and cardiomyopathy (n=1).	N.S.	Enlarged mitochondria with parallel or concentric cristae.
	Deltoid	37 years (same individual as above)	CPEO, cerebella ataxia and cardiomyopathy (n=1).	N.S.	Unusually large mitochondria ranging from 5-8 μm in greatest diameter with cristae usually located at the periphery of the organelle and rectangular inclusions; cross sections of the PCI structures disclosed well-organized arrays of tubules oriented in parallel rows with a diameter of 70-80 A, with a lumen of 30-40 A, and interspace between the tubules of 20-30 A, arranged in a helical pattern; abnormal mitochondria almost completely replaced by dense rectangular inclusions and occasionally showed complete transition to crystalline structures obscuring the original mitochondrial morphology.
Shibasaki *et al.* (1973)	Deltoid	60 years	Late onset myopathy; marked atrophy of shoulder girdle and proximal upper limb,	N.S.	Elongated, giant mitochondria up to 5 μm in greatest diameter, particularly in the SS region; PCIs including lattice pattern, four-fold array, or amorphous form.

			pelvic and proximal lower limb muscles; mild atrophy of distal lower limb muscles (n=1).		
Crosby and Chou (1974)	Left bicep	10 years	[Pediatric] Leigh disease (n=1).	N.S.	Enlarged mitochondria (in cross section); whirled cristae membranes; electron dense spheroid bodies; electron-lucent mitochondrial matrix spaces; complex, convoluted membrane systems; PCI within cristae membrane.
Black *et al.* (1975)	Anterior tibialis or Quadriceps	30 years	Mitochondrial disorder, RRFs, and ptosis (n=1).	N.S.	Enlarged mitochondria with "wavy" cristae and central electron dense granular material; round dense osmiophilic inclusions; occasional lipid inclusions and concentric cristae.
Karpati *et al.* (1975)	Quadriceps	11 years	[Pediatric] KSS biopsied before and after Carnitine supplementation (n=1).	N.S.	PCI; concentric cristae; swollen mitochondria.
McLeod *et al.* (1975)	Quadriceps (vastus lateralis)	27 years	Mitochondrial myopathy (n=1).	N.S.	PCI with parallel bands of amorphous material surrounded by a membrane; mitochondria with "empty" electron-lucent spaces; amorphous material between the mitochondrial membranes; mitochondria containing "empty space" surrounded by double membranes.
Bastiaensen *et al.* (1979)	Ocular and skeletal	>30 years [review]	PEO plus.	N.S.	[Review] Aggregates of swollen mitochondria with parallel or concentric cristae.
Linden and Ansink (1979)	Gastrocnemius	11 years	[Pediatric] KSS. Ptosis, mental and physical retardation, dysarthria (n=1).	N.S.	PCI; large mitochondria.
Fitszsimons and Tyer (1980)	Left deltoid	10 and 17 years	Mitochondrial myopathy. Myopathy, scoliosis, respiratory failure. (n=2)	N.S.	Rectangular inclusions, PCI, amorphous material and concentric cristae in mitochondria.
Fukuhara *et al.* (1980)	Quadriceps femoris	21 years	MERRF. Myoclonic jerk, seizures, hypotonia, ataxia (n=1).	N.S.	Electron-lucent homogenous matrix space; enlarged mitochondria; markedly proliferated IMM; PCIs.
Land *et al.* (1981)	Left deltoid	14 years	[Pediatric] Mitochondrial myopathy, opthalmoplegia (n=1).	N.S.	Mitochondria with "finger-print" like patterns (i.e., densely packed parallel cristae); concentric cristae.
Shah *et al.* (1982)	Quadriceps	N.S.	KSS, polymyositis,	N.S.	PCIs (30-45 nm long and 22-23 nm wide); round or oval swollen

			neurogenic atrophy, mitochondrial myopathy.		mitochondria; presence of various inclusions; densely packed or tubular cristae formation; concentric cristae or “lamellar bodies”; parallel destruction of cristae and presence of amorphous material.
Holliday *et al.* (1983)	N.S.	18 and 26 years	Mitochondrial myopathy, encephalopathy (n=2).	N.S.	Rectangular or curvilinear PCIs composed of four parallel lamina within a boundary membrane.
Mitsumoto *et al.* (1983)	Deltoid	11 to 49 years (m=34.5)	CPEO with RRF (n=8).	N.S.	Mitochondria with absent cristae; irregular vacuoles; PCIs; concentric cristae; dark inclusion; whirl formation.
Muller-Hocker *et al.* (1983)	N.S.	N.S.	PEO (n=8).	N.S.	Enlarged mitochondria with high cristae content; concentric cristae and PCIs.
Prick *et al.* (1983)	N.S.	2 and 5 years	[Pediatric] Alper’s disease (n=2).	N.S.	Aggregates of enlarged mitochondria with PCIs in SS region.
Sarnat *et al.* (1983)	Quadriceps femoris, deltoid, extensor digitorum longus of the forearm (post mortem)	3 weeks and 4 months	[Pediatric] Mitochondrial myopathy, cerebro-hepato renal (Zellweger) syndrome (n=2).	N.S.	Electron dense granules in mitochondrial matrix; myelin figures, degeneration and other degenerative changes (e.g. membrane rupture) to mitochondria.
Sengers *et al.* (1983)	Quadriceps	4 years	[Pediatric] Mitochondrial myopathy, carnitine deficiency (n=1).	N.S.	Large mitochondria with densely packed or whirled cristae; granular or fibrillary electron dense material in intercristal space.
Hayes *et al.* (1984)	Intercostal muscle	20 years	Mitochondrial myopathy, bilateral ptosis, muscle bulk normal, mild diffuse weakness (n=1).	N.S.	SS mitochondria with concentric cristae and inclusions; central droplets of neutral or osmiophilic lipid or areas of central necrosis.
Kennaway *et al.* (1984)	N.S.	17 years	Mitochondrial myopathy, lactic acidosis (n=1).	N.S.	Abnormally large mitochondria some with PCIs.
Bresolin *et al.* (1985)	Quadriceps	2, 3, 6 and 7 months	[Pediatric] Mitochondrial myopathy, hypertonia and severe limb weakness, tendon and pharyngeal weakness absent (n=1).	N.S.	Large mitochondria with irregular or concentric tubular cristae.
Muller-Hocker *et al.* (1985)	N.S.	12 years	[Pediatric] Mitochondrial myopathy, excercise	N.S.	Swollen mitochondria with PCIs.

			induced muscle weakness and pain, tachycardia and dyspnoea (n=1).		
Niebrój-Doblosz *et al.* (1985)	Biceps brachii and quadriceps	7 years	[Pediatric] KSS. Biceps and quadriceps weakness, mental retardation, progressive limb weakness (n=1).	N.S.	Giant mitochondria; PCIs; concentric cristae.
Fischer *et al.* (1986)	Quadriceps	17 years	Mitochondrial enchephalomyopathy, seizures, myoclonic contractures, retarded motor and speech development (n=1).	N.S.	Small mitochondria with swollen matrix; concentric cristae or "concentric laminated bodies".
Lehmann *et al.* (1986)	Deltoid	44 years	Myopathy with rimmed vacuoles, mild shoulder girdle weakness, exercise intolerance (n=1).	N.S.	PCIs of Type I and II.
Stadholders and Sengers (1987)	N.S.	N.S.	Mitochondrial myopathy (KSS, MELAS, MERRF)	N.S.	[Review] PCIs and concentric cristae; suggests model of PCI formation; classify 2 types of PCI (Type I, Type II); suggests different types of PCI for different fibre types.
Van Ekeren *et al.* (1987)	N.S.	6 days	Hereditary mitochondrial hypertrophic cardiomyopathy (n=1).	N.S.	Mitochondria with vesicular inclusions; matrix crystals.
Columbo *et al.* (1988)	Left quadriceps	27 years	Mitochondrial occuloskeletal myopathy (n=1).	N.S.	PCIs; globular dense bodies; cristae running concentrically.
Dias-Tosta (1988)	N.S.	N.S.	CPEO. Sporadic muscle weakness (n=10), familial isolated myopathy (n=9), myopathy with retinopathy, cerebellar ataxia, or peripheral neuropathy (n=15).	N.S.	PCIs; concentric cristae; "parking lot" and "intramural type" inclusions.
Federico *et al.*	Quadriceps	N.S.	LHON (n=3).	N.S.	Enlarged mitochondria with PCIs.

(1988)					
Mizusawa *et al.* (1988)	Rectus femoris or tibialis	46 and 48 years	Familial mitochondrial myopathy, pptic atrophy, muscle wasting, weakness (n=2).	N.S.	Aggregates of mitochondria with PCIs; electron dense globular bodies; concentric cristae.
Kim *et al.* (1989)	Left deltoid	53 years	CPEO. Mild proximal limb weakness (n=1)	N.S.	PCIs; irregularly orientated cristae.
Paulus *et al.* (1989)	Left quadriceps	33 years	Mitochondrial encephalomyopathy with perivacuolar inclusions, bilateral hearing loss, seizures, cerebral atrophy, moderate muscle atrophy (n=1).	N.S.	Small osmiophilic rod-like inclusions; piles within round or oval vacuoles (perivacuolar inclusions).
Rivner *et al.* (1989)	N.S	25 years	KSS. Cerebellar and cortical atrophy, mild ataxia and generalised weakness of proximal and distal muscles (n=1).	N.S.	Deformed internal architecture; PCI arrays; concentric cristae or “cristae arranged circumferentially”.
Suzuki *et al.* (1989)	Quadriceps	35 years	Mitochondrial encephalomyopathy, general muscle atrophy, psychiatric disturbance (n=1).	N.S.	Enlarged mitochondria with PCIs.
Arruda *et al.* (1990)	Quadriceps	32 and 34 years	Mitochondrial myopathy with myoclonic epilepsy. Myoclonic jerks and seizures (n=2).	N.S.	Enlarged mitochondria.
Haginoya *et al.* (1990)	Quadriceps (vastus femoris)	8-43 years (m=25)	MERRF and MELAS. Mixed, myoclonic seizure, ataxia, stroke-like episodes, ptosis (n=3).	N.S.	Aggregated mitochondria in areas of segmental COX deficiency.
Korenke *et al*. (1990)	N.S.	2 weeks - 9 years (m=2 years)	[Pediatric] Mitochondrial myopathy. Mixture; respiratory insufficiency, hypotonia, motor	N.S.	Abnormally small and large mitochondria; PCIs; polymorphy; altered cristae.

			retardation and feeding problems (n=8).		
Schapira *et al.* (1990)	Quadriceps (vastus lateralis)	14 years	Mitochondrial myopathy. Weakness of limbs and trunk, high CK.	Defect in protein transport? Molecular cause N.S.	Disordered "labyrinth" cristae with electron dense and granular inclusions.
Sumegi *et al.* (1990)	N.S.	45 days	[Pediatric] COX deficiency.	N.S.	Swollen mitochondria, and often "tennis-racket" like mitochondria (swollen at one end); mitochondria with honeycomb cristae.
Takeda *et al.* (1990)	Extraocular muscles	14 to 30 years (m=20)	MELAS and MERRF. Mixed symptoms (n=3).	N.S.	Mitochondria of irregular shape with tubule-vesicular cristae; morphological changes more prominent in MELAS than MERRF. No PCI.
Kim *et al.* (1991)	N.S.	16 and 22 years	Mitochondrial myopathy. Severe respiratory dysfunction, mild myopathy.	N.S.	Sickle shaped mitochondria containing curvilinear PCI, regular PCIs.
McKelvie *et al.* (1991)	Quadriceps (vastus lateralis)	48 years (n=1)	KSS. Opthalmoplegia, limb weakness, ataxia (n=1).	3.5Kb single mtDNA deletion[i]	PCIs in subsarcolemmal aggregates of mitochondria.
Letellier *et al.* (1992)	Deltoid	1 week to 4 months (m=2 months)	[Pediatric] Mitochondrial myopathy. Mixture of symptoms (n=6).	N.S.	Enlarged and swollen mitochondria.
Linda *et al.* (1992)	N.S.	N.S.	Mitochondrial myopathy. MELAS (n=3), Marinesco-Sjogren syndrome (n=7) and KSS (n=2).	mtDNA mutations N.S.	PCIs; pleoconial mitochondria; enlarged "megamitochondria"; thickening, unfolding, and parallelization of cristae; concentric cristae or "concentric lamellar cristae"; augmented matrix space; amorphous inclusion bodies.
Modi *et al.* (1992)	Biceps brachii	20 years	Mitochondrial myopathy. Proximal myopathy, cardiomyopathy, bilateral deafness and ptosis.	N.S.	Laminated PCIs.
Telerman-Toppet *et al.* (1992)	N.S.	8 weeks	[Pediatric] COX deficiency and mtDNA depletion (n=1).	N.S.	PCIs; abnormal spatial arrangement of mitochondrial cristae.
Angelini *et al.*	Biceps and	19 and 25	Hypertrophic	Dystrophin	Enlarged mitochondria with irregular cristae.

(1993)	quadriceps	years	cardiomyopathy with mitochondrial myopathy. Weakness in upper limb girdle muscles and Gower's signs and waddling gait, no cerebellar abnormalities (n=2).	and mtDNA deletions ruled out. Cause N.S.[i]	
Coquet *et al.* (1993)	N.S.	15 and 17 years	MERRF. Myoclonic jerks, epileptic seizures, ataxia, deafness, lower limb weakness (n=2).	*m.8344A>G*[a] $tRNA^{Lys}$	PCIs; concentric cristae.
Reichmann *et al.* (1993)	Biceps brachii	53 years	KSS. Mild generalized muscle weakness and exercise intolerance, diabetes, slowly progressive ataxia (n=1).	Multiple deletions[b] (causative mutation N.S.)	PCIs; concentric cristae.
Ionasescu *et al.* (1994)	Quadriceps (vastus lateralis)	9 years	[Pediatric] MERRF. Progressive proximal weakness (n=1).	*m.15990A>G*[a] $tRNA^{Pro}$	PCIs.
Norby *et al.* (1994)	Quadriceps (vastus medialis)	15 years	[Pediatric] KSS. Epileptic seizures, ataxia, myopathy (n=1).	11Kb single mtDNA deletion[b]	Enlarged mitochondria with PCIs.
Stadhouders *et al.* (1994)	N.S.	N.S.	CPEO, KKS, MELAS	N.S.	PCIs (Types I and II).
Gilbert and Ems (1996)	N.S.	21 months	Pearson's syndrome. Pancreatic atrophy, enlarged kidneys, metabolic acidosis, high blood lactate and hypomagnesemia (n=1).	N.S.	Aggregated SS and IMF mitochondria; concentric cristae, enlarged mitochondria with disrupted membranes; central follicular (granular) matrix.
Melberg *et al.* (1996)	Quadriceps (vastus lateralis) or bicularis oculi	16 to 63 years (m=52 years)	Dominant PEO. Ocular myopathy, hypogonadism (n=14).	Dominant genetic cause N.S.	Densely packed cristae; size variation; longitudinally or circular cristae; crystalloid-like alterations.

Toscano *et al.* (1996)	N.S.	73 to 75 years (m=74 years)	Late-onset mitochondrial neuropathy. Muscle weakness and cramps, ataxia, exercise intolerance (n=3).	No mtDNA mutations found[b,c]. Genetic cause N.S.	PCIs, enlarged or bizarrely shaped mitochondria.
van Domburg *et al.* (1996)	Soleus, quadriceps, ocular rectus superior	25 to 36 years (m=30 years)	CPEO plus. Ocular myopathy, encephalomyopathy, sensory neuropathy, ataxia, polyneuropathy (n=6).	No evidence of maternal inheritance, common point mutations and deletions ruled out[i]. Genetic cause N.S.	PCIs, mitochondria with deranged cristae; concentric cristae.
Wada *et al.* (1996)	Quadriceps femoris	11 weeks	[Pediatric] Mitochondrial myopathy. Muscular hyoptonia, profound acidosis, difficulty suckling, no muscle weakness (n=1).	N.S.	Enlarged mitochondria with sparse cristae; concentric cristae.
Heimann-Patterson *et al.* (1997)	N.S.	4 to 63 years (m=28 years)	Family with mitochondrial myopathy. Exercise intolerance, proximal lower limb weakness in first decade of life (n=11).	mtDNA deletions and common point mutations ruled out, a number of non-pathogenic point mutations found[d]. Genetic cause N.S.	Uneven and electron dense cristae; globular inclusions.
Kim and Chi (1997)	Deltoid	22 and 23 years	KSS. Neck and proximal limb weakness, severe ptosis, AV block.	Single mtDNA deletion[1,c]	PCIs, enlarged mitochondria with distorted cristae.
Smith *et al.* (1997)	Quadriceps	N.S.	Mother of MELAS patient, with insulin dependent	*m.3243A>G*[a] $tRNA^{Leu}$	Pleomorphic mitochondria; concentric cristae; electron-dense bodies.

			diabetes (n=1).		
Takahashi *et al.* (1998)	Quadriceps femoris	9 months	[Pediatric] Leigh disease. Generalized hypotonia at birth, apnea attacks, irregular breathing, poor head control (n=1).	*m.8993T>G*[a] MT-ATP6	Variably sized mitochondria; aberrant cristae.
Castro-Gago *et al.* (1999)	Deltoid	Fetus	Hydranencephalic-hydrocephalic syndrome in association with mitochondrial encephalomyopathy.	Common mtDNA point mutations and deletions ruled out[i]. Genetic cause N.S.	Enlarged SS mitochondria; abnormal cristae (honey-comb-like).
Kyriacou *et al.* (1999)	N.S.	6 days to 10 years (m=2 years)	[Pediatric] Mitochondrial enchephalomyopathy. Hypotonia and psychomotor retardation (n=5), multisystemic (n=2), Pearson syndrome (n=1), Leigh disease (n=1). (Adult) Myalgia and proximal limb weakness (n=8), PEO (n=3).	N.S.	Pleomorphic mitochondria; simplified cristae; vesicular cristae.
Melegh *et al.* (1999)	N.S.	5 months	Mitochondrial enchephalomyopathy. Myoclonic jerk, uncoordinated eye movement (n=1).	Multiple mtDNA deletions[b]. Nuclear mutation N.S.	Enlarged mitochondria with no or few cristae.
Carta *et al.* (2000)	Quadriceps (rectus medialis)	48 years	CPEO (n=1)	Single common mtDNA deletion[1,b]	PCIs; “onion-like” concentric cristae, “ghost-like” mitochondria (devoid of cristae).
Makino *et al.* (2000)	N.S.	N.S.	Leigh syndrome. Hypotonia, necrotic lesions in basal ganglia and brainstem (n=1).	*m.8993T>G*[a] MT-ATP6	Enlarged mitochondria.

Wang *et al.* (2000)	N.S.	9 years	No prominent muscle weakness or hypotonia, but wobbling gait early on. Proximal limb myopathy 1 month prior to biopsy (n=1).	N.S.	Loss of matrix and cristae.
De Kremer *et al.* (2001)	N.S	N.S.	[Pediatric] Barth-syndrome like disorder, marked muscle weakness.	*m.3243A>G*[d] $tRNA^{Leu}$	Round swollen mitochondria; fine fibrillary matrix; poorly define cristae.
Higashikata *et al.* (2001)	Biceps brachii	80 years	MELAS. Cardiomyopathy.	*m.3243A>G*[a] $tRNA^{Leu}$	Aggregates of enlarged mitochondria with PCIs.
Rollins *et al.* (2001)	N.S.	1 to 70 years (m=12.5 years)	Mitochondrial cytopathy (n=113)	Mutation of "maternal inheritance" N.S.	PCI; enlarged mitochondria.
Vogel (2001)	N.S.	N.S.	Mitochondrial myopathy	N.S.	[Review] Swollen, elongated, devoid of cristae, PCIs.
Fagiolari *et al.* (2002)	N.S.	27 to 73 years (m=55 years)	CPEO (n=7), PEO and ptosis (n=7), myopathy (n=1).	Multiple mtDNA deletions[b] due to *ANT1* mutation – *p.114A>P* and *p.98L>P*[i]	Mitochondrial proliferation and PCIs.
Fillano *et al.* (2002)	N.S.	2 to 12 years (m=7 years)	HEADD syndrome (hypotonia, epilepsy, autism, and developmental delay) (n=3)	Multiple mtDNA deletions[c] (nuclear cause N.S.) or 7.4Kb single mtDNA deletion[c]	Stacked cristae; electron dense deposits.
Kim *et al.* (2002)	Biceps brachii	18 Years	MERRF. Myoclonic epilepsy, myopathy, ataxia, dysarthria (n=1).	*m.8344A>G*[e] tRNALys	PCI; concentric cristae.
Marín-García *et al.* (2002)	N.S.	15 years	PEO (n=1)	Multiple mtDNA	Vacuolated cristae; variation in size and morphology.

				deletions[b]	
Nevo *et al.* (2002)	Quadriceps	11 to 26 months (m=16 months)	[Pediatric] Mitochondrial myopathy. Motor deterioration, dyspneic, muscle weakness, bilateral ptosis.	*TK2* mutation causing mtDNA depletion[i]	Pleomorphic mitochondria; enlarged mitochondria; concentric cristae or "concentric lamellae".
Kyriakides *et al.* (2003)	N.S.	6 days to 18 months (m=6 months, n=19), 19 to 75 years (m=42 years, n=14)	Mitochondrial encephalomyopathies: myopathic, multisystemic or CPEO. Pediatric (n=19) and adult (n=14).	N.S.	Mitochondrial dysmorphology more common in children than adults and vice versa.
Uusimaa *et al.* (2003)	N.S.	10 months	Alpers-Huttenlocher-like disease (n=1)	*m.7706G>A*[d] MT-COII	Enlarged mitochondria; variable shape and size.
Mierau *et al.* (2004)	Quadriceps	8 years	[Pediatric] Lactic acidosis, proximal weakness, cognitive delay.	N.S.	PCIs; enlarged or abnormally small; concentric cristae; parking lot type inclusions; spherical electron dense inclusions.
Patterson *et al.* (2004)	N.S.	16 years	KSS.	5Kb mtDNA deletion[f]	PCIs.
Carta *et al.* (2005)	Quadriceps (rectus medialis)	42 to 75 years (m=63 years)	CPEO and LHON (n=3)	Single common mtDNA deletion[1,i]	"Ghost" mitochondrial profiles (lack of cristae) with partial to complete matrix emptying rearrangement of the cristae with an "onion ring-like" appearance
Coulbault *et al.* (2005)	N.S.	10 months	[Pediatric] Psychomotor retardation, failure to thrive, hypotonia, hepatocellular dysfunction, thrombocytopenia.	*m.5693T>C*[e], $tRNA^{ASN}$	PCIs; stacked cristae.

			Multiple organ failure (lethal) (n=1).		
Dinopoulos *et al.* (2005)	Quadriceps	1 to 15 months (n=9 months)	[Pediatric] Hypotonia, myoclonic epilepsy, cardiomyopathy, psychomotor regression, failure to thrive, lactic acidosis (mixed) (n=4).	*NDUFS2 c.237T>C*, *NDUFS8 c.236C>T* and *c.302G>A*, *NDUFVI c.175C>X* and *c.1268C>T* mutations (CI)[i]	Concentric cristae or "concentric laminated bodies"; osmiophilic mitochondria.
Enns *et al.* (2005)	Quadriceps (vastus lateralis) and deltoid	6 weeks to 5 years (m=1.5 years)	Electron transport chain abnormalities, RRFs. (n=7)	N.S.	Enlarged mitochondria; swelling with electron-lucent matrix space; proliferation of mitochondria; elongated and branched.
Güçer *et al.* (2005)	N.S.	4 months and 9 years	[Pediatric] Seizures, ptosis, failure to thrive, high serum lactate and pyruvate, RRF (n=2).	Single common mtDNA deletion[1,b]	Increased matrix density and cristae; SS mitochondrial accumulation.
Karppa *et al.* (2005)	Quadriceps (vastus lateralis) or tibialis anterior	16 to 70 years (m=45 years)	MELAS	*m.3243A>G*[i] $tRNA^{Leu}$	PCIs (Types I and II); variation in size and ultrastructure.
Kyriacou *et al.* (2005)	N.S.	6 days to 18 years (median= 4 years, n=31) and 19 to 75 years (median= 46 years, n=17)	Mitochondrial encephalomyopathy (n=48).	N.S.	Elongated and enlarged mitochondria more common in children than adults; subsarcolemmal aggregation of mitochondrial (RRF) more common in adults.
Pulkes *et al.* (2005)	N.S.	16 and 23 years	MERRF. Proximal upper and lower limb weakness, ataxia, seizures and myoclonus (n=2).	*m.7472_insC*[i] $tRNA^{Ser}$	Type 2 fibres larger and dense matrix components and contain either or both type 1 or 2 crystalline intra-membranous inclusions. Type 1 myofiber mitochondria, have many large and abnormal forms, show a more orderly arrangement of their cristae, a lesser

					quantity of less dense matrix, and only type 1 intra-membranous crystalline inclusions.
Stenqvist *et al.* (2005)	Quadriceps (vastus lateralis)	10 years	[Pediatric] MELAS. Mild central and cortical brain atrophy, encephalopathy, no mention of myopathy (n=1).	*m.3271T>C*[f] $tRNA^{Leu}$	Dense granular inclusions, parallel cristae arrays, open matrix spaces.
Zeharia *et al.* (2005)	N.S.	19 years	Mitochondrial myopathy (n=1).	Autosomal recessive *PUS1*[d]	PCIs.
Cardaioli *et al.* (2006)	Quadriceps	31 years	Deafness, mental retardation, brain atrophy (n=1).	*m.7472insC*[e] $tRNA^{ser\ (UCN)}$ and *m.7472A>C*[e] $tRNA^{ser\ (UCN)}$	Swollen mitochondria with reduced cristae and PCIs.
Deschauer *et al.* (2006)	N.S.	66 years	Exercise intolerance, walking difficulty, muscle cramps, hearing impairment, mild myopathy and peripheral neuropathy (n=1).	*m.622G>A*[d] $tRNA^{Phe}$	Enlarged mitochondria with PCIs.
Miles *et al.* (2006)	N.S.	2 weeks to 21 years (median= 2.7 years)	KSS (n=4), Leigh syndrome (n=2), lethal infantile COX deficiency (n=2), MERRF (n=1), encephalopathy with (n=72) and without myopathy (n=46).	N.S.	PCIs; abnormal patterns of cristae; concentric cristae or “circular cristae” and fingerprint cristae; abnormal matrix density.
Saneto and Boulding (2006)	N.S.	11 years	[Pediatric] Muscle weakness, hypercarbia, lactic acidosis, absent deep tendon reflexes, respiratory difficulty (n=1).	*m.3243A>G*[i] $tRNA^{Leu}$	Enlarged rounded mitochondria; distorted cristae; electron dense inclusions.
Thajeb *et al.*(2006)	N.S.	65 years	Oculopharangyl somatic myopathy, bilateral ptosis and difficulty swallowing	Single mtDNA deletion[c,d] and homoplasmic *m.5814T>C*[d]	“Parking lot” type PCIs.

			(n=1).	tRNA^{Cys}	
Wabbels *et al.* (2007)	M. levator palpebrae, and/or the M. orbicularis oculi	4 to 81 years (m=40 years)	Adult/child Ptosis/CPEO (n=21).	N.S.	PCIs; concentric and wavy cristae; pleomorphy; intermitochondrial granules.
Perry *et al.* (2008)	Quadriceps	3 days	[Pediatric] Sengers syndrome. Bilateral ptosis, hypotonia, trace reflexes, skeletal muscle myopathy and cardiomyopathy (n=1).	N.S.	Diffuse dysmorphic mitochondria.
Pronicki *et al.* (2008)	Quadriceps (vastus lateralis)	9 months to 12 years (m=3.5 years)	[Pediatric)] Leigh Syndrome. Motor regression, bulbar symptoms, difficulty walking, hypotonia, failure to thrive, floppiness, disturbed eye movement (n=21).	*SURF1*[i] mutation	Enlarged or elongated mitochondria; dark matrix with densely packed, concentric lamellae cristae; mitochondrial matrix displaced by amorphous granular material; small electron-dense osmiophilic granules.
Yerdelen *et al.* (2008)	Biceps brachii	38 years	KSS. Delayed motor and mental development, arrhythmia (n=1).	N.S.	PCIs; swollen mitochondria with few electron dense cristae; osmiophilic and electron-dense structures.
Abu-Amero *et al.* (2009)	N.S.	34 years	MELAS (n=1)	No mtDNA mutations or POLG mutations. Genetic cause N.S.	Mitochondria with parallel cristae and PCIs, osmiophilic inclusions and mitochondrial vacuoles.
DeBrosse *et al.* (2009)	Deltoid	67 years	CPEO. Ptosis, mild upper limb weakness, mild memory difficulty and imbalance (n=1).	N.S.	PCIs; dystrophic mitochondria.
Yau *et al.* (2009)	Quadriceps	14 years	[Pediatric] KSS, short stature, mental deficiency, lower limb	Single 7.2Kb mtDNA deletion[c]	PCIs; irregular structure and cristae; central core-like fibres (IMF mitochondrial depletion).

			weakness, mild ataxic gait (n=1).		
Ali *et al.* (2010)	Triceps brachii	62 years	CPEO. Diplopia, no muscle weakness (n=1).	Single mtDNA deletion[1,b,c,d]	PCIs (Type I); swollen rounded mitochondria.
Ascaso *et al.* (2010)	N.S.	48 years	KSS. Bilateral ptosis, proximal muscle weakness and RRFs (n=1).	Single mtDNA deletion[1b,c,d]	Large atypical mitochondria; round electron dense bodies.
Cardenas and Amato (2010)	N.S.	14 years	[Pediatric] Alpers disease. Neuropathalogical degeneration of cerebral grey matter (n=1).	*POLG* mutations (compound heterozygous) *c.911T>G* (p. L304R), *c.1174C>G* (p.L392V) and a duplication (pR1081dup)[f]	Reduced mitochondrial content, absence of cristae, vacuolization.
Chi *et al.* (2010)	Quadriceps	1 month to 15 years (median= 15 months, n=69)	[Pediatric] Leigh disease (n=6).	*m.8993T>G* (n=3) MT-ATP6, *m.8993T>C* MT-ATP6 (n=1), *m.10191T>C* MT-ND3 (n=1) and *m.8344A>G* (n=1)[c,d,e]	Tubular cristae; swollen mitochondrial accumulation; variable shapes; concentric "whirl" cristae; inclusion bodies.
			[Pediatric] MELAS (n=4).	*m.3243A>G* $tRNA^{Leu}$ (n=4)[c,d,e]	
			[Pediatric] Pearson syndrome (n=1)	6 Kb mtDNA deletion (n=1)[c,d,e]	

			Mixed mitochondrial disease (n=58)	Genetic cause N.S.	
Han *et al.* (2010)	Rectus femoris	4 to 48 years (m=N.S)	Spinocerebellar ataxia type 7. Unsteady gait, visual problems, cerebellum and brain stem atrophy (n=34).	*SCA7* mutation[c] CAG repeat	Mitochondrial with tubular or absent cristae.
Herrero-Marti *et al*. (2010)	N.S.	50 years	MELAS MERRF overlap (n=1)	*m.5521G>A*[g] $tRNA^{Trp}$	PCIs.
Lang *et al.* (2010)	Ocular medial rectus	47 and 67 years	CPEO, ptosis, exercise intolerance and mild myopathy (n=2).	Multiple mtDNA deletions[i] (nuclear mutation not defined)	Enlarged mitochondria; hypertrophic concentric lamellar cristae.
Baskin *et al.* (2011)	N.S.	9 years	Mitochondrial myopathy. Myopathic findings by electromyography, deafness, ocular and neurological findings (n=1).	*NPHS3*[g] mutation	Abnormal mitochondrial shape and cristae patterns.
Cenacchi *et al.* (2011)	Quadriceps, Tricep, deltoid	19 to 79 years (m=56 years)	Mitochondrial myopathy (=14).	N.S.	Accumulation of SS mitochondria; rounded, elongated, or cup-shaped mitochondria; abnormally large or “mega-mitochondria”; concentric cristae; lipid-dense; PCIs in matrix.
Conway *et al.* (2011)	gastrocnemius	29 years	MELAS. Seizures, hearing loss (n=1).	*m.3243A>G*[i] $tRNA^{Leu}$	Abnormally arranged cristae and aberrant electron density.
Shaaf *et al.* (2011)	N.S.	3 and 8 years	Optic nerve atrophy, hypotonic, ataxia (n=2).	*OPA1* mutation *c.2708_2711delTTAG* (p.V903GfsX3) and *c.1146A>G* (p.I382M)[d]	Mitochondrial with dense osmiophilic bodies.

Blakey *et al.* (2012)	Quadriceps	21 years	Neuropathy and leukoencephalopathy, walking difficulties, distal numbness, muscle wasting of hands and distal lower limbs (n=1).	*MPV17* mutation[d] causing 12.5Kb mtDNA deletion[c]	Enlarged, “parking lot” type inclusions.
Bostan *et al.* (2012)	Deltoid	52 years	Ptosis, ataxia, neuropathy, gastroparesis, myopathy (n=1).	*POLG* mutation[i]	PCIs.
Gotz *et al.* (2012)	N.S.	5 days	[Pediatric] Fatal neonatal lactic acidosis (n=1).	*m.7453G>A*[d] $tRNA^{Ser}$	Enlarged and swollen mitochondria, concentric cristae.
Kendall *et al.* (2012)	Multiple	N.S.	Multiple mitochondrial disorders.	N.S.	[Review] Previous reports suggest electron microscopy is not a good diagnostic tool. However other sources report the frequency of 30-44% of aberrant mitochondrial morphology in pediatric mitochondrial disease and conclude its usefulness.
Pfeffer *et al.* (2012)	Levator palpebrae	34 to 72 years (m=52 years)	CPEO (n=8)	*POLG1* (n=1), single mtDNA deletion (n=4), multiple mtDNA deletion (n=1, NS (n=2)[b,c,e]	Large mitochondrial aggregates, pleomorphism, various inclusions.
Roefs *et al.* (2012)	Orbicularis	46 to 64 years (m=58 years)	Progressive bilateral ptosis and generalised muscle weakness (n=3).	Single mtDNA deletion[b,c]	Enlarged mitochondria; densley packed parallel cristae; electron dense inclusions.
Baric *et al.* (2013)	Deltoid	17 years	Elevated CK, mild myopathy in brachial muscles.	*m.5522G>A*[c,g] $tRNA^{Trp}$	Swollen globular looking mitochondria, occasional branching and angular OMM.
Lopez *et al.* (2013)	Tibialis anterior	22 years	[Pediatric] Fatal infantile mitochondrial DNA depletion (n=1).	*TK2* mutation[c,g]	Elongated mitochondria with PCIs.
Lu and Huang (2013)	Biceps brachii	1 to 13 years (m=8	MELAS (n=6)	*m.3243A>G*[i] $tRNA^{Leu}$	Globualar looking mitochondrial shape elongated with swollen regions and PCIs.

		years)			
Nolte *et al.* (2013)	N.S.	16 and 17 years	Seizures, myoclonic jerk, PEO (n=2).	*POLG1 c.2243G>C* (p.W748S) and *c.1879C>T* (p.R627W)[g]	Elongated mitochondria with "globoid" inclusions (amorphous lipid-like); SS mitochondrial accumulation or "aggregates".
Polimeno *et al.* (2013)	N.S.	N.S.	Mitochondrial myopathy (other symptoms N.S.).	N.S.	PCIs; mitochondria assuming bizarre and/or giant forms.
Siriwardena *et al.* (2013)	N.S.	15 months	Sengers syndrome (n=1)	*AGK* mutation[g]	Pentagonal mitochondrial crystals with a dense outer layer.
Yuan *et al.* (2013)	N.S.	51 and 54 years	RRF, rimmed vacuoles, muscle weakness in facial, cervical and proximal muscles, wasting of shoulder girdle (n=2).	*m.8344A>G*[d] $tRNA^{Lys}$	PCIs; Mitochondrial proliferation, concentric cristae.
Zhao *et al.* (2013)	Biceps brachii	66 years	CPEO, RRF and diffuse muscle weakness (n=1)[g].	Large 4Kb mtDNA mutation	PCIs.
Chen *et al.* (2014)	N.S.	44 years	CPEO, ptosis, diplopia, bulbar paresis, inflammatory myopathy, neck muscle weakness (n=1).	Single mtDNA deletion[1,h]	PCIs preferentially in SS mitochondria.
Hopmann *et al.* (2014)	N.S.	72 years	Mitochondrial myopathy, muscle atrophy and proximal weakness of arms trunk and legs (n=1).	Multiple mtDNA deletions[b,c]	"Parking lot" inclusions; swollen aggregated mitochondria; loss of cristae.
Chatfield *et al.* (2015)	N.S.	2 months	Mild enchephalomyopathy, diffusion of the perirolandic white matter (n=1).	*HSD10* mutation[g] *c.740A>G* (p.N247S)	Loss of cristae; swollen vacuolated mitochondria.
Nozuma *et al.* (2015)	N.S.	32 and 76 years	Mitochondrial myopathy, limb weakness and	16 non-pathogenic	Accumulation of mitochondria, vacuolated mitochondria.

			general fatigue, high CK, myalgia (n=2).	mtDNA alterations[i]: Pathogenic N.S.	

*Age at biopsy for EM study
AV: Atrioventricular
CPEO: Chronic progressive external opthalmoplegia
IMF: Intermyofibrillar
KSS: Kearns-sayer syndrome
MELAS: Mitochondrial encephalomyopathy, lactic acidosis and stoke-like episodes
mtDNA: Mitochondrial DNA
MERRF: Myoclonic epilepsy and ragged red fibres
N.S.: Not specified
PCI: Paracrystalline inclusion
PEO: progressive external opthalmoplegia
RRF: Ragged-red fibers
SS: Subsarcolemmal
[1]: common large-scale deletion, 4977bp in length between two 13-bp direct repeats at positions *m.13447-13459* and *m.8470-8482.*
Genetic diagnostic methodology: [a]Restriction site mutation assay; [b]Southern blot, [c]PCR, [d]Sanger sequencing, [e]RFLP, [f]Solid phase mini sequencing, [g]Sequencing, [h]Next generation sequencing, [i]Not specified

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