Mitochondrial Disease and PMM

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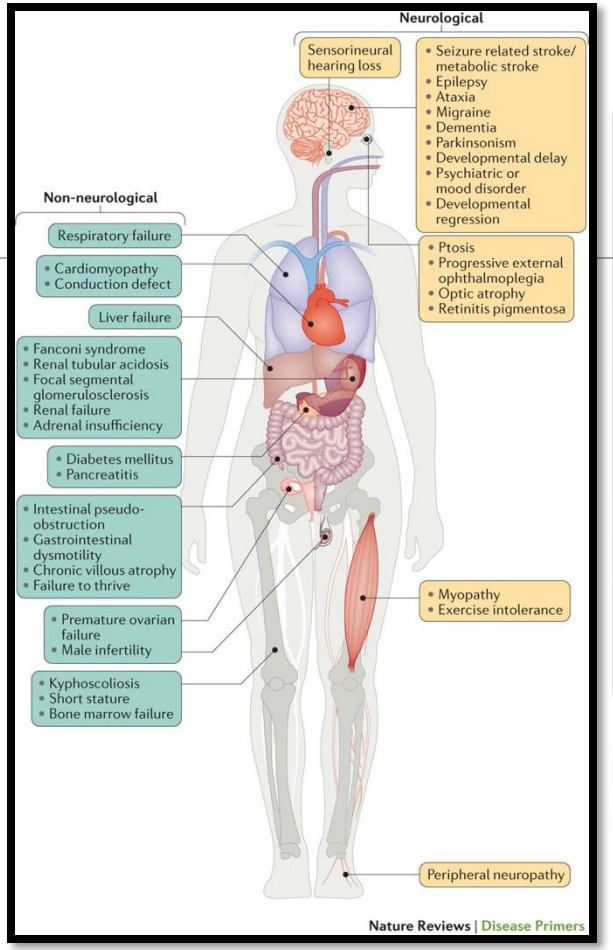
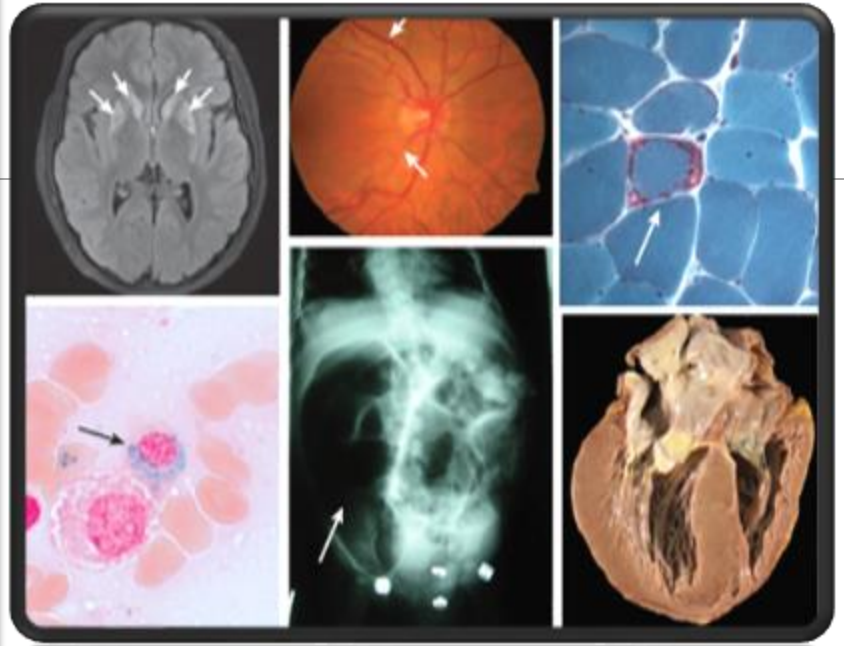
Overview of mitochondrial disease

"Any symptom, any organ, any age, any mode of inheritance"

- Munnich & Rustin (Am.J.Med.Genet. 2001, 106:4-17)





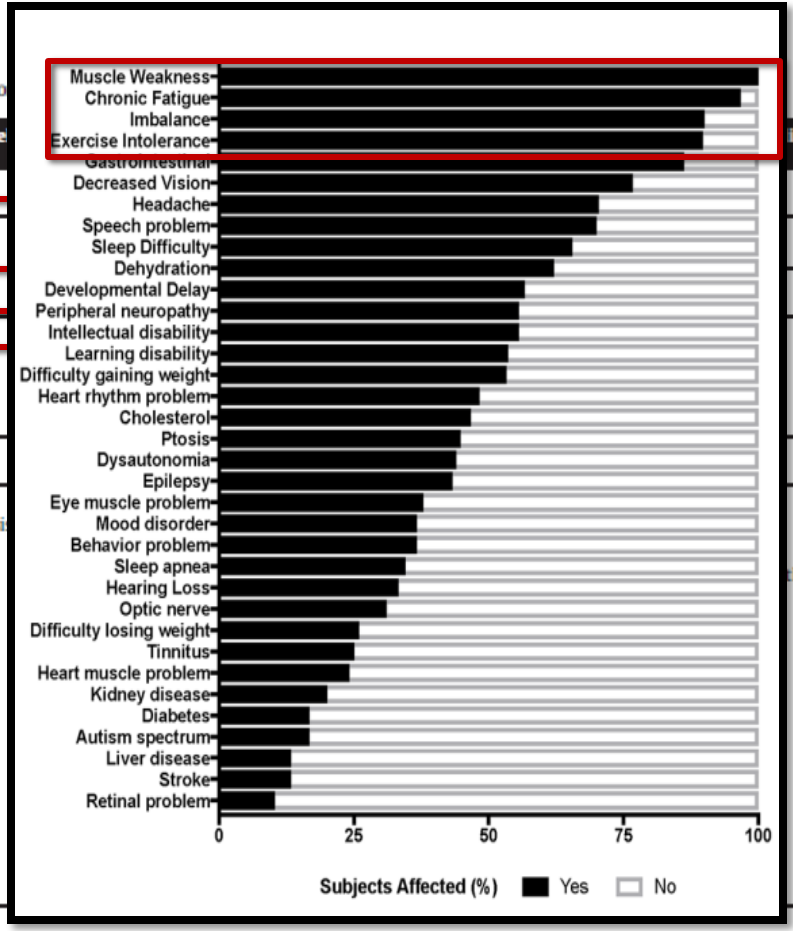
Vafai and Mootha, Nature 2012

Clinical Manifestations in Percent (number positive/number recorded)			
Manifestation	Overall	Pediatric	Adults
Weakness	41.8 (308/737)	41.6 (138/332)	42.0 (170/405)
Developmental Delay	41.2 (319/775)	72.8 (273/375)	11.5 (46/400)
Exercise Intolerance	40.4 (289/716)	34.8 (110/316)	44.8 (179/400)
Fatigue	35.5 (262/738)	26.2 (85/325)	42.9 (177/413)
Hypotonia	35.4 (260/735)	65.1 (231/355)	7.6 (29/380)
Myopathy	34.1 (255/747)	31.0 (105/339)	36.8 (150/408)
Seizures	31.1 (237/763)	42.5 (151/355)	21.1 (86/408)
Ataxia	28.7 (216/753)	32.5 (112/345)	25.5 (104/408)
Hearing Loss	26.3 (194/739)	16.4 (54/330)	34.2 (140/409)
Ptosis	25.9 (199/769)	18.6 (65/350)	32.0 (134/419)
Dysphagia	22.0 (162/738)	26.7 (90/337)	18.0 (72/401)
Thinness	19.8 (144/726)	23.2 (77/332)	17.0 (67/394)
Migraine Headaches	18.2 (131/720)	9.7 (31/319)	24.9 (100/401)
Hearing Loss	17.3 (124/718)	13.2 (42/319)	20.6 (82/399)
Growth Delay	16.0 (113/708)	27.2 (88/323)	6.5 (25/385)
Depression	15.9 (111/700)	3.8 (12/316)	25.8 (99/384)
Anxiety	15.3 (107/699)	10.5 (33/315)	19.3 (74/384)
Ophthalmoparesis	15.3 (111/727)	6.5 (21/324)	22.3 (90/403)
Mental Retardation	13.6 (97/715)	25.1 (79/315)	4.5 (18/400)
Motor Regression	13.1 (96/733)	23.8 (81/341)	3.8 (15/392)
Total number	878	402	476

NAMDC Registry accessed 01/2017

Most frequent patients/parents reported sympto

Constitutional		Musculoske		iac	Other	
Chronic fatigue	61%					
Temperature instability	48%	Myalgia			Anxiety	25%
Exercise intolerance	42.5%					
Difficulty gaining weight	12%	Myoglobinuria		18%	Depression	19%
		Rhabdomyolysi		11%	Thyroid disease	9%
Growth delay	6%			6%	Diabetes	7%
Cachexia	5%			thy 4%	Short stature	7%
Lipoma	3%				Parathyroid disease	7%
					Hypogonadism	2%
					Delayed puberty	3%
					Renal tubulopathy	2%



PLOS ONE | https://doi.org/10.1371/journal.pone.0197513

Clinical Trial

https://www.tctmd.com/

Clinical Trial

- Study of the ways disease affect patients
- What potential process may stop, slow or
on

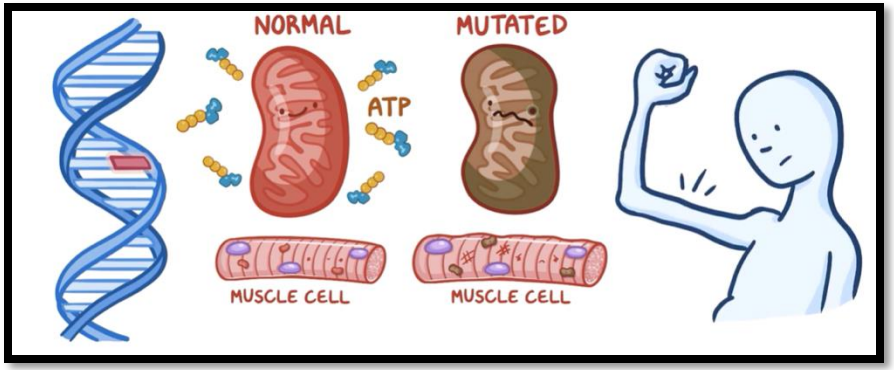
Food and Drug Administration (FDA)

- Experiments to see how the therapy may work and interact with other parts of the body

Primary Mitochondrial Myopathy

Consortium of International Experts in Mitochondrial Disease

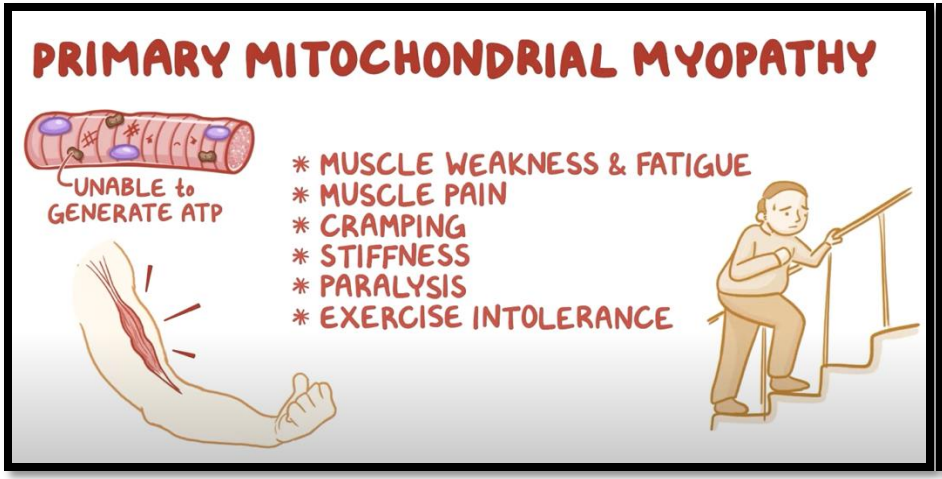
- Primary Mitochondrial Myopathy (PMM) refers to a subset of primary mitochondrial disease that predominantly but not exclusively affect skeletal muscles.

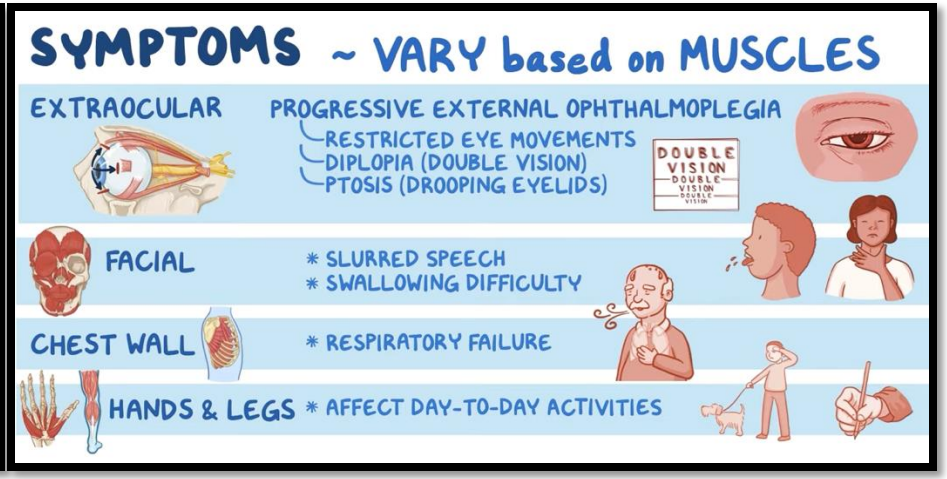


Osmosis.org

Neuromuscul Disord. 2017 December ; 27(12): 1126–1137. doi:10.1016/j.nmd.2017.08.006.

Primary Mitochondrial Myopathy





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Primary Mitochondrial Myopathy

PMM includes several clinical syndromes:

- Chronic Progressive External Ophthalmoplegia (CPEO)
- Chronic Progressive External Ophthalmoplegia plus (CPEO +)
- isolated mitochondrial myopathy

Isolated mitochondrial myopathy (adults)

- Progressive axial and proximal limb weakness
- Difficulty swallowing (dysphagia)
- Respiratory failure (rare)
- Distal muscle weakness (rare)
- Fatigue, Exercise Intolerance, Pain
- Spasms, myoglobinuria, triggered by exercise (cyt b or CoQ10 deficiency) (rare)

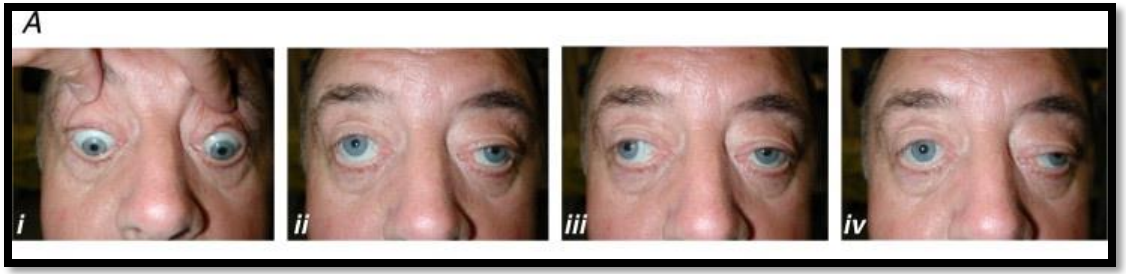
Isolated mitochondrial myopathy (Children)

- Floppiness
- Breathing issues
- Abnormal reflexes
- More rapidly progressive weakness
- Difficulty swallowing (dysphagia)
- Distal muscle weakness
- Spasms, myoglobinuria

https://www.fairfaxfamilyfun.com/

Chronic Progressive External Ophthalmoplegia: CPEO

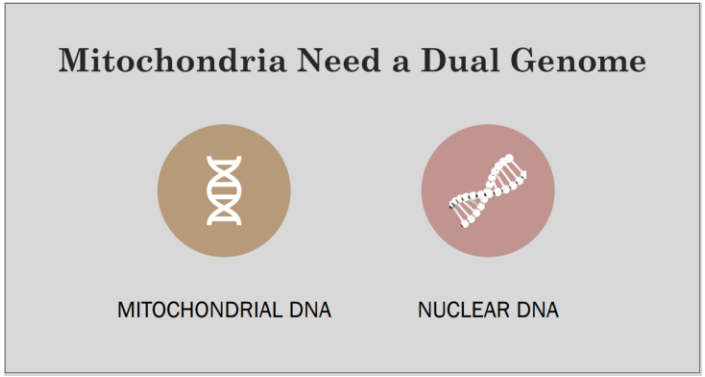
- Commonest phenotype of PMM (2/3)
- Bilateral eyelid droopiness (presenting symptom)
- Slowly progressive limitation of eye movement (ophthalmoplegia) in all directions of gaze
- Sometimes double vision



Chronic Progressive External Ophthalmoplegia plus: CPEO +

- Other slow skeletal muscle involvement (hip and shoulder girdle)
- Fatigue, Exercise Intolerance, Pain
- Difficulty swallowing
- Rarely respiratory failure

Primary Mitochondrial Myopathy



Sporadic (random chance)

Mitochondrial DNA single deletion (1/3 of patients)

Maternally inherited (mitochondrial DNA)

(i.e. m.3243A>G, m.8344A>G)

Mendelian inheritance (from one or both parents)

Primary Mitochondrial Myopathy

Consortium of International Experts in Mitochondrial Disease

- Late-onset mild isolated mitochondrial myopathies might be difficult to diagnose (secondary mitochondrial dysfunction)
- Secondary involvement of mitochondria observed in multiple neuromuscular diseases is not considered PMM.

Neuromuscul Disord. 2017 December ; 27(12): 1126–1137. doi:10.1016/j.nmd.2017.08.006.

Diagnostic Evaluation

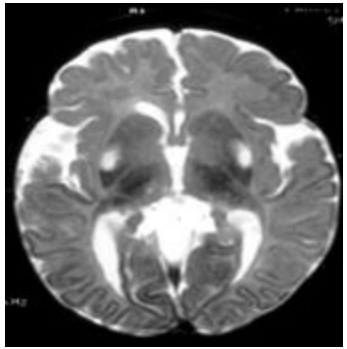
Symptoms
Family history

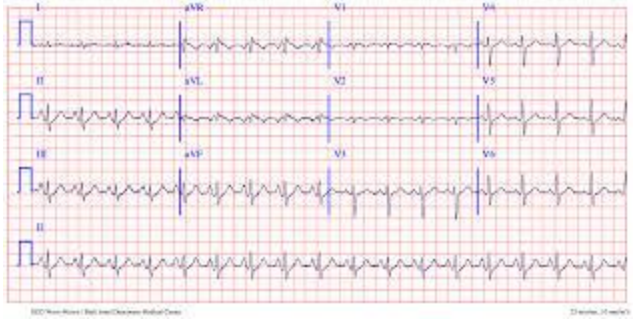
Testing:

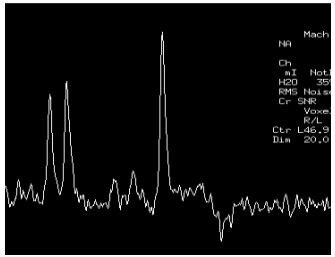
- CPK or CK
- Lactic acid
- GDF15

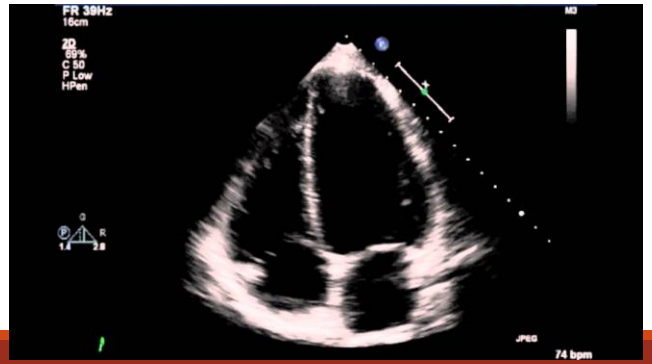
Diagnostic Evaluation

Evaluating organ involvement



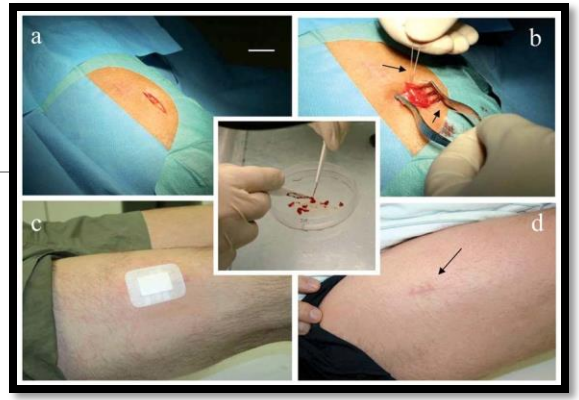




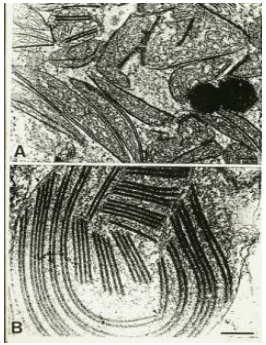


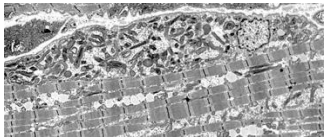
Diagnostic Evaluation

- Tissue pathology (muscle)

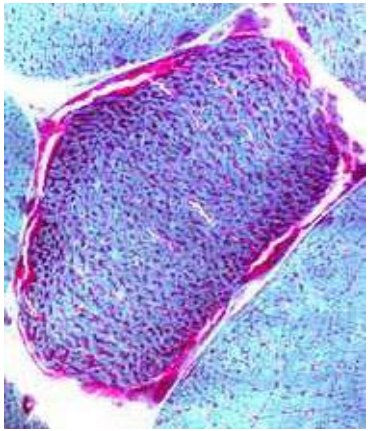


EM

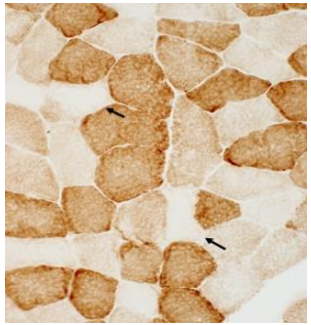




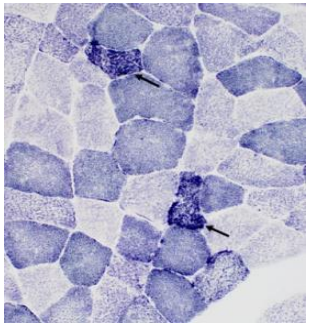
Histochemistry



RRF

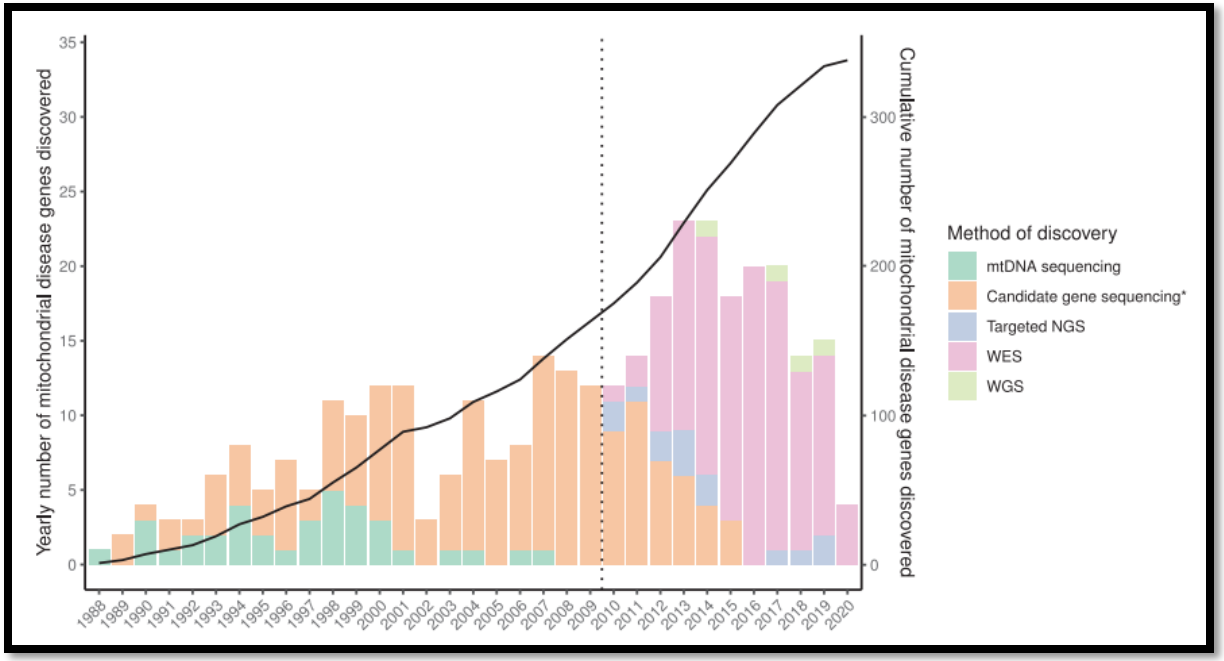


COX



SDH

Diagnostic Evaluation



Complicated genotypes

mDNA (37 genes)
nDNA (~400 genes)

~1500 various genes

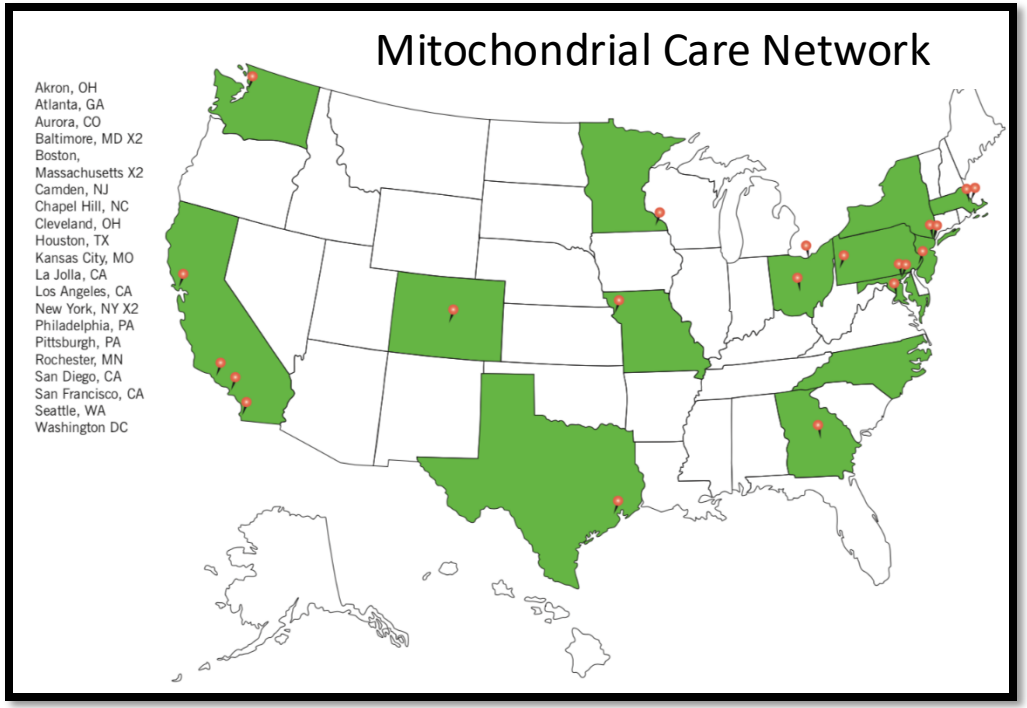
Diagnostic Evaluation

The diagnostic yield of next generation sequencing in suspected mitochondrial disease.

	Genes analysed	Publication	Size of cohort	Biochemical confirmation	Age group	mt-DNA analysis	Diagnostic rate
Panel	<500	Calvo et al. [22]	60	+	P	Included*	22 (13)
		DaRe et al. [23]	148	+/-	P and A	Included*	9% (13)
		Legati et al. [24]	125	+/-	P and A	Included*	15% (19)
	>500	Calvo et al. [25]	42	+	P	Included*	31% (13)
		Vasta et al. [26]	26	+/-	P	Excluded prior	23% (6)
		Lieber et al. [27]	84	+/-	P and A	Included*	7% (6)
		Panel summary	485				14% (70)
WES	20,000	Haack et al. [30]	10	+	P	Included*	70% (7)
		Taylor et al. [31]	53	+	P	Excluded prior	54% (28)
		Ohtake et al. [32]	104	+	P	Excluded prior	43% (45)
		Wortmann et al. [33]	109	–	P	Excluded prior	39% (42)
		Legati et al. [24]	10	+	P and A	Included*	60% (6)
		Kohda et al. [34]	142	+	P	Included*	35% (49)
		Pronicka et al. [35]	113	–	P	Included*	59% (67)
		Puusepp et al. [36]	28	–	P	Included*	57% (16)
		Theunissen et al. [38]	63	–	P and A	Included*	62% (39)
		WES Summary	632				47% (299)

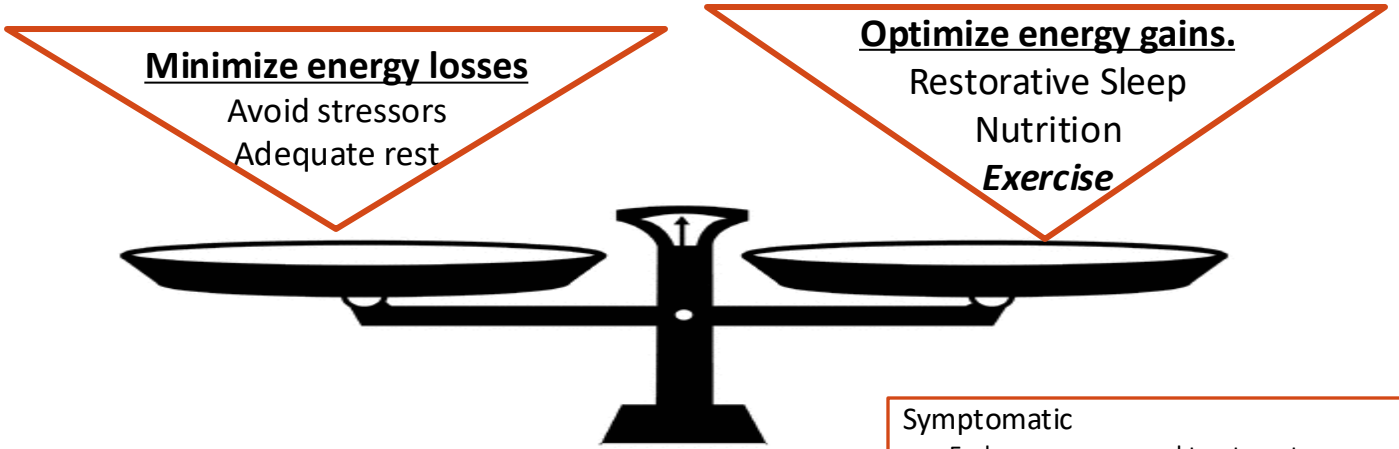
S.L. Stenton and H. Prokisch / EBioMedicine 56 (2020) 102784

Other diagnostic barriers



https://www.mitonetwork.org/

Treatment and Management



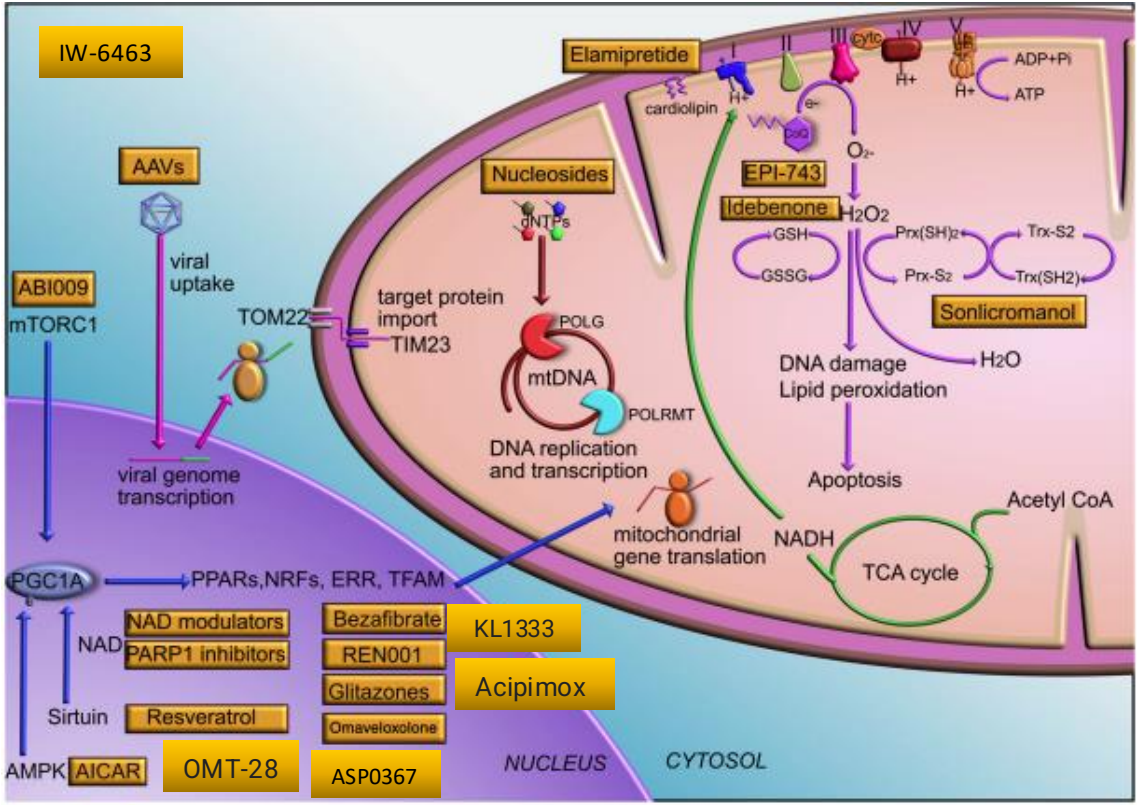
- Avoid environmental toxins: (ETOH, smoking, drugs..)

Symptomatic
- End organ survey and treatment

Supportive
- Overall disease burden
- Supplements (CoQ10)

Non curative

What is new in research and development?

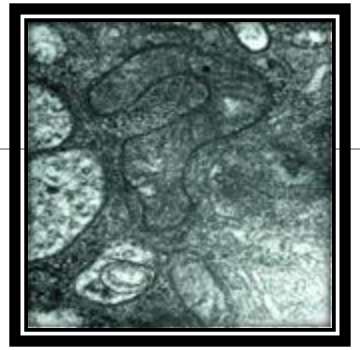


J Inherit Metab Dis. 2020;1–20.

Take home points

- NO MOLECULAR CONFIRMATION → NO PMM
- MITOCHONDRIAL DISEASE ≠ PMM
- MUSCLE SYMPTOMS WITH A COMPLEX CLINICAL PICTURE ≠ PMM

Thank you, and any questions?



For any questions:

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