At the crossroad of mitochondrial disease and mitochondrial dysfunction

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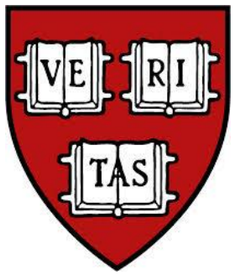
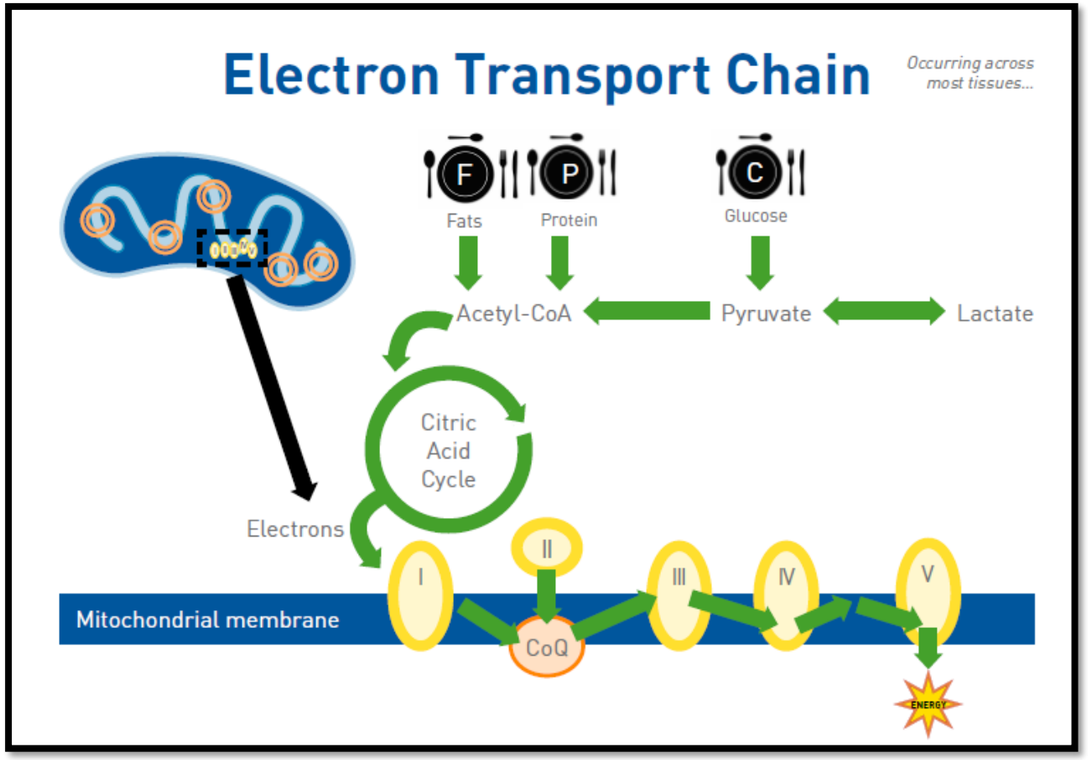
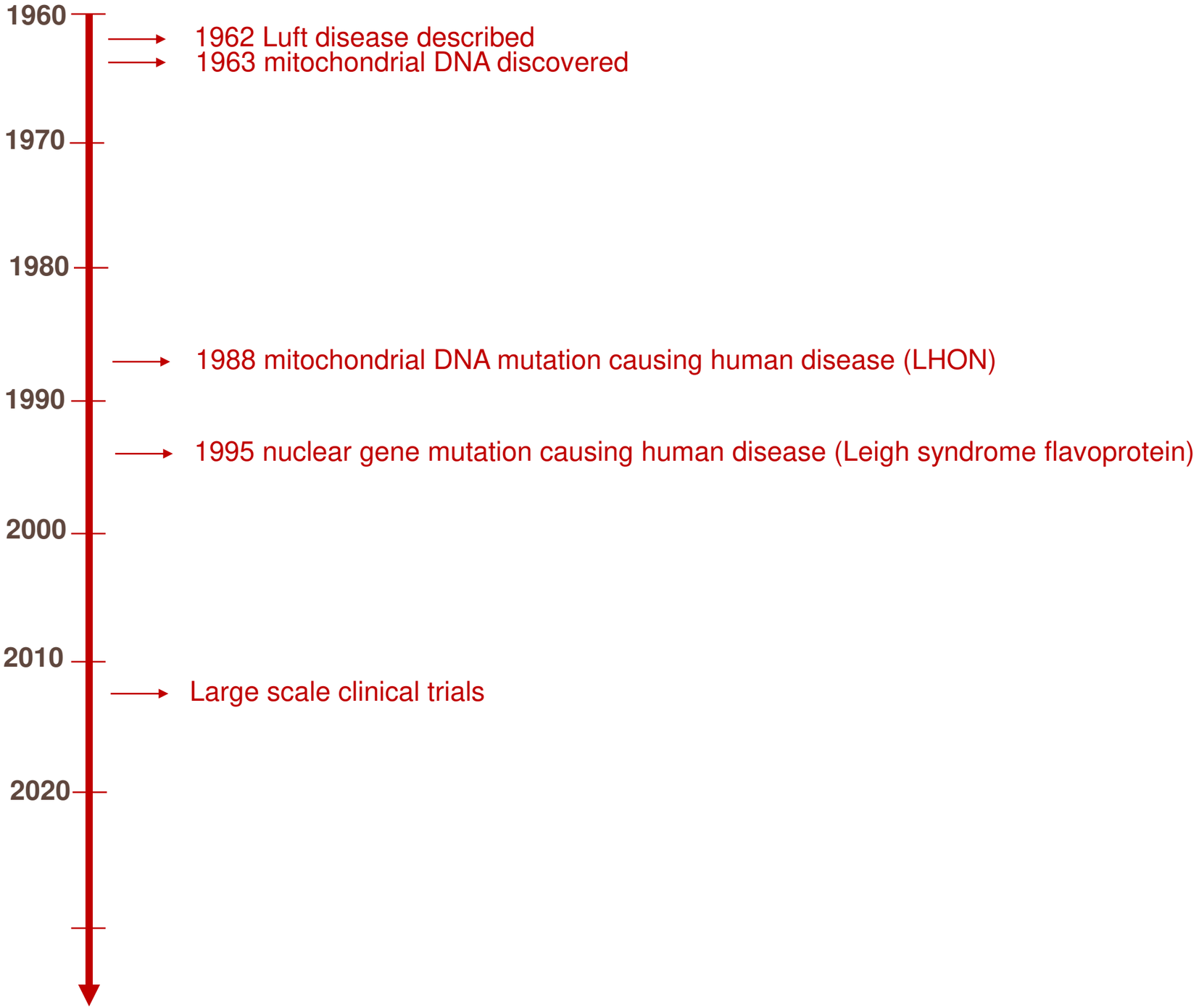


Mitochondrial diseases (Mito)

“The challenge is the extraordinary clinical spectrum of mitochondrial diseases, which all too often leads practitioners to either underdiagnose ("What is this complex disorder?") or over diagnose ("This disorder is so complex that is must be mitochondrial!").

From the NAMDC mission statement (www.namdc.org)




1960
1962 Luft disease described
1963 mitochondrial DNA discovered
1970
1980
1988 mitochondrial DNA mutation causing human disease (LHON)
1990
1995 nuclear gene mutation causing human disease (Leigh syndrome flavoprotein)
2000
2010
Large scale clinical trials
2020

The Clinical Criteria Era

Table *Mitochondrial disease criteria (simplified version for bedside use)**

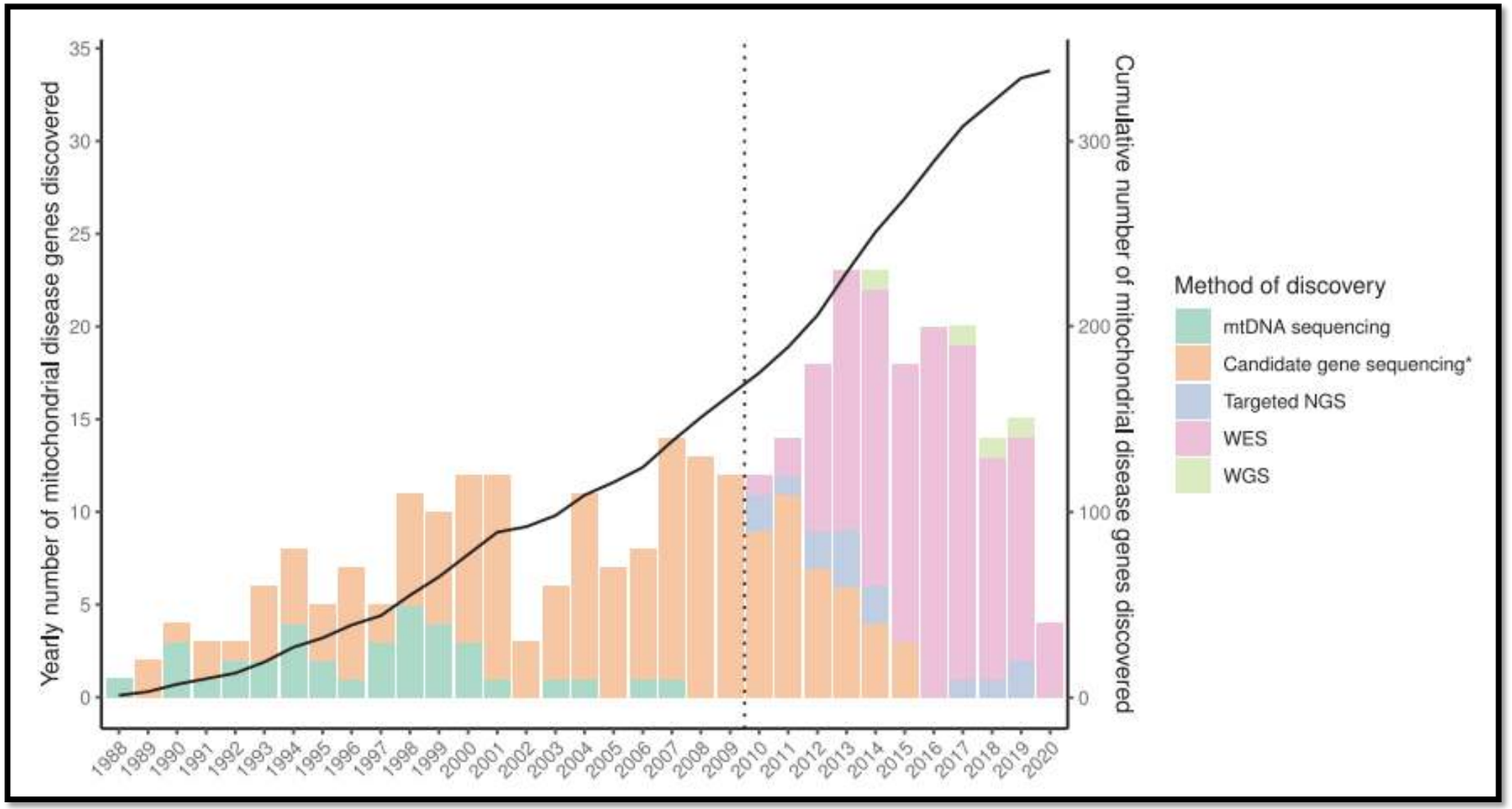
I. Clinical signs and symptoms, 1 point/symptom (max. 4 points)

A. Muscular presentation (max. 2 points)	B. CNS presentation (max. 2 points)	C. Multisystem disease (max. 3 points)	II. Metabolic/imaging studies (max. 4 points)	III. Morphology (max. 4 points)
Ophthalmoplegia†	Developmental delay	Hematology	Elevated lactate†	Ragged red/blue fibers‡
Facies myopathica	Loss of skills	GI tract	Elevated L/P ratio	COX-negative fibers‡
Exercise intolerance	Stroke-like episode	Endocrine/growth	Elevated alanine†	Reduced COX staining‡
Muscle weakness	Migraine	Heart	Elevated CSF lactate†	Reduced SDH staining
Rhabdomyolysis	Seizures	Kidney	Elevated CSF protein	SDH positive blood vessels†
Abnormal EMG	Myoclonus	Vision	Elevated CSF alanine†	Abnormal mitochondria/EM†
	Cortical blindness	Hearing	Urinary TA excretion†	
	Pyramidal signs	Neuropathy	Ethylmalonic aciduria	
	Extrapyramidal signs	Recurrent/familial	Stroke-like picture/MRI	
	Brainstem involvement		Leigh syndrome/MRI†	
			Elevated lactate/MRS	

* Score 1: mitochondrial disorder unlikely; score 2 to 4: possible mitochondrial disorder; score 5 to 7: probable mitochondrial disorder; score 8 to 12: definite mitochondrial disorder.

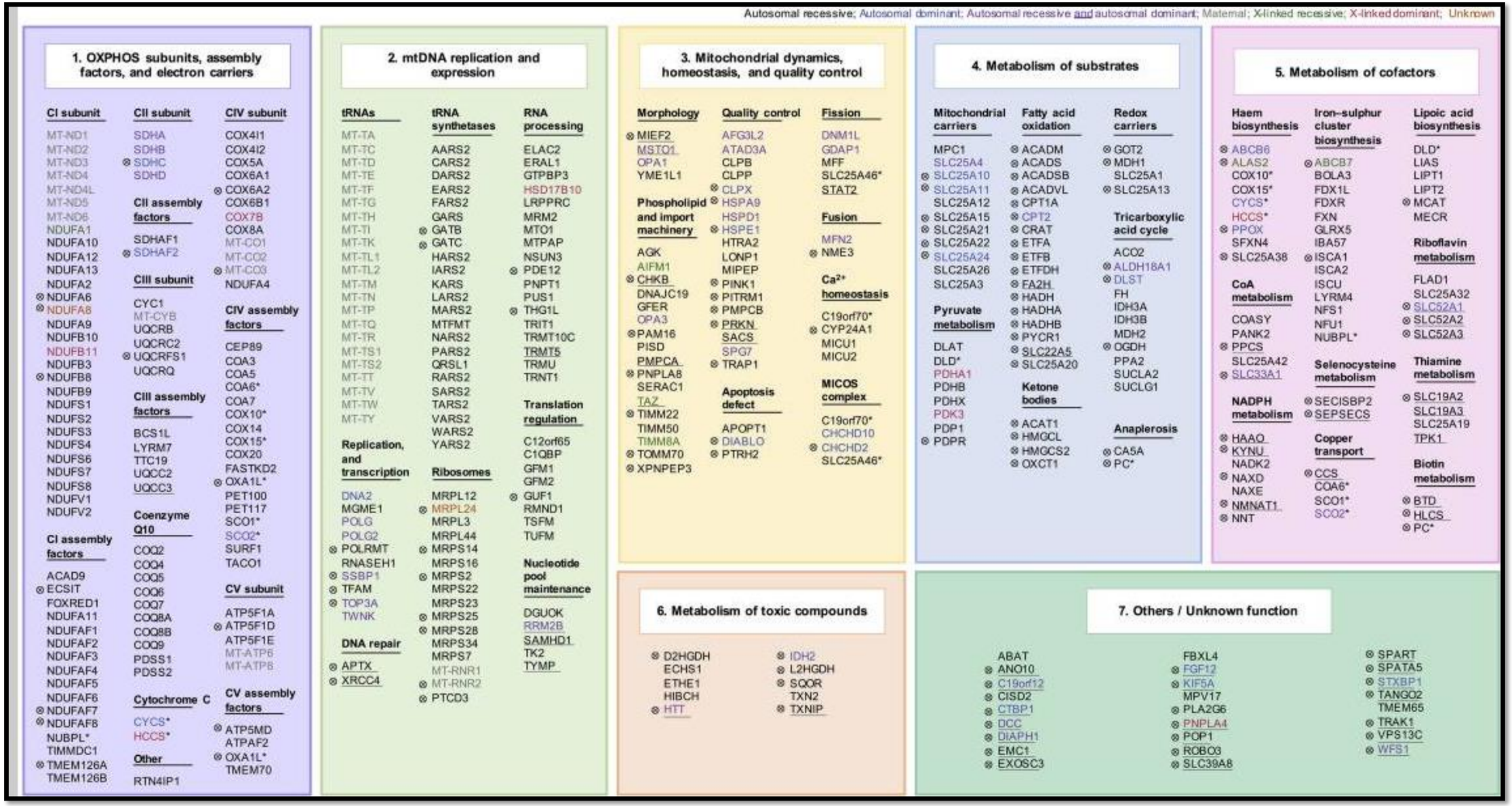
Morava et al. Mitochondrial disease criteria: diagnostic applications in children. Neurology. 2006 Nov 28;67(10):1823-6. PMID: 17130416.

The Genetic Era



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

The Genetic Era



Schlieben et al. Front Cell Dev Biol. 2020 Nov 26;8:600079.

The Genetic Era

Table 1 Differential diagnosis of selected phenotypes commonly associated with mitochondrial disease

Phenotype	Mitochondrial cause	Limited differential diagnosis
Dystonia	Leigh syndrome, deafness-dystonia syndrome, other mitochondrial encephalomyopathies	Biotinidase deficiency, thiamine transporter deficiency 2, *ADAR* mutations (Aicardi- Goutières syndrome 6), organic acidaemias (especially glutaric aciduria type I), NBIA, acute (viral) necrotising encephalopathy, mutations in *NUP62*, *RANBP2* and *PDE8B*, primary genetic dystonias
Epileptic encephalopathy	Alpers-Huttenlocher syndrome, many other mitochondrial disorders	Many genetic epileptic encephalopathies, including Dravet syndrome and *KCNQ2* mutations, Pyridoxine dependent epilepsies (Antiquitin deficiency, PNPO deficiency), viral encephalitis
Progressive myoclonic epilepsy	MERRF	Ramsay Hunt syndrome, Unverricht-Lundborg disease, Lafora body disease, sialidosis, *PRICKLE1* mutations
Leukoencephalpathy	Complex I deficiency, Complex II deficiency, SURF1 deficiency (rarely), disorders of mitochondrial translation and Fe-S cluster assembly	Vanishing white matter disease, lysosomal storage disorders, Canavan disease, Alexander disease, Pelizaeus-Merzbacher(-like), hypo/dysmyelination
Ataxia	*ADCK3* mutations, ataxia-neuropathy syndromes, for example, SCAE, MIRAS, MERRF, NARP, disorders of coenzyme Q_{10} biosynthesis	Spinocerebellar ataxias, CAPOS syndrome
Demyelination	MNGIE	ADEM, multiple sclerosis
Peripheral neuropathy	Mutations in *POLG*, *MPV17*, *KARS* and *SURF1*; part of multisystem disease in many mitochondrial disorders, for example, MNGIE	Other non-mitochondrial genetic causes of Charcot-Marie-Tooth syndromes, riboflavin transporter deficiency, toxic neuropathies, critical illness
Ptosis and ophthalmoplegia	PEO, KSS, MNGIE, MELAS	Some congenital myopathies, pseudo upgaze impairment in *OPMD*, horizontal gaze palsy and scoliosis (*ROBO3* mutation)
Optic neuropathy	LHON, ADOA, Leigh syndrome	Toxic optic neuropathy (eg, methanol, cyanide, tobacco)
Hypertrophic cardiomyopathy with lactic acidosis	Complex I deficiency, *TMEM70* mutations, Sengers syndrome (AGK deficiency), disorders of mitochondrial translation	Viral infection
Dilated cardiomyopathy with lactic acidosis	Barth syndrome, disorders of mitochondrial phospholipid remodelling, other mitochondrial cardiomyopathies	Viral infection
Exocrine pancreatic insufficiency	Pearson syndrome	Cystic fibrosis
Diabetes and deafness	MIDD, other mtDNA mutations	Type II diabetes mellitus with incidental non-syndromic deafness
Sideroblastic anaemia	Pearson syndrome, MLASA, TRNT1 deficiency, *PUS1* or *YARS2* mutations	Blackfan-Diamond syndrome, Schwachman-Diamond syndrome, X linked sideroblastic anaemia
B cell immune deficiency	TRNT1 deficiency	Primary immunodeficiency disorder
Liver failure	Mitochondrial DNA (mtDNA) depletion syndromes,	NBAS, LARS and IARS deficiencies, viral infection, lysosomal storage disorders, other syndromic genetic conditions
Renal tubulopathy/failure	Pearson and Kearns-Sayre syndromes, *RMND1*-related disease	Gitelman syndrome, Fanconi Bickel (*SLC2A2* mutations) syndrome, other syndromic genetic conditions
Myopathy	Part of multisystem disease in many mitochondrial disorders, especially mtDNA depletion syndromes	Congenital muscular dystrophies, myositis, many other disorders
Rhabdomyolysis	Mitochondrial myopathies (eg, *MTCO1*, *MTCO2*, *MTCO3* and *MTCYB* mutations)	*LPIN1* mutations, fatty acid oxidation defects (VLCAD, LCHAD), TANGO deficiency, glycolytic defects, toxic, postexercise
Low copper	Cytochrome oxidase deficiency	Menkes, *SLC33A1* mutations
Complex multisystem disorders	Many mitochondrial disorders, particularly in childhood	Congenital disorders of glycosylation, peroxisomal disorders, lysosomal storage disorders, other syndromic genetic conditions

Table 2 Mitochondrial dysfunction identified in select other genetic disorders

Disorder	Mitochondrial defect	Reference by PubMed ID number
AOA1 (*APTX* mutations)	Coenzyme Q_{10}	15699391
Desminopathy	CS, mtDNA depletion (35%)	26097489
Dravet syndrome (*SCN1A* mutations)	Variable OXPHOS deficiencies	20392657; 21906962
EXOSC3 and *EXOSC8* related diseases	Low Complex I and pyruvate dehydrogenase activities, low mtDNA copy number, increased expression of mitochondrial genes	28687512; 24989451
GLUT1 deficiency	Complex I	22156785
GM3 synthase deficiency	Respiratory chain dysfunction in fibroblasts and liver	22990144
LCHADD	Complex III, COX	16417669
Limb immobilisation	COX and CS	19654872
Lysosomal diseases: GM1-gangliosidosis, mucopolysaccharidosis IIIC, multiple sulfatase deficiency, Krabbe disease, Gaucher disease, Niemann Pick disease type C	Multiple OXPHOS deficiencies attributed to excessive production of mitochondrial reactive oxygen species and dysregulated calcium homeostasis with mitochondria-induced apoptosis and neurodegeneration	28132808
MADD (*ETFDH*, *ETFA* or *ETFB* mutations)	Complex I and II deficiencies; Riboflavin and Coenzyme Q_{10} responsive	17412732
Molybdenum cofactor deficiency	COX	16417669
MTHFR mutations	Complex I deficiency	21131308
Multiple carboxylase deficiency	Complex III	16417669
NBIA (PKAN)	Complex III	16417669
Neonatal haemochromatosis	Complex III (liver)	16417669
Neuroferritinopathy (*FTL1*)	Complex I or multiple Complex deficiency	17142829
NPHS3 (PLCE1 deficiency)	COX	21365190
Neuronal Ceroid Lipofuscinosis (*CLN2* and *CLN3*-related)	Partial deficiency in fatty acid oxidation enzymes and the storage of subunit c of mitochondrial ATP synthase in fibroblasts	8971698
ORAI1 related disease	Impaired lipid metabolism and fatty acid oxidation in skeletal muscle, heart and liver due to abnormal store-operated Ca^{2+} entry	28132808
Organic acidemias	Coenzyme Q_{10}, multiple OXPHOS deficiencies and free radical induced oxidative damage	21329767; 28753922; 28753922
Ras/MAPK pathway mutations	Variable OXPHOS deficiencies	26097489
Rett syndrome (*MECP2* mutations)	Variable OXPHOS deficiencies	26741492
SCAR10	Coenzyme Q_{10}	25182700
Spinal muscular atrophy	Complexes I-IV, mtDNA depletion	12557011; 25844556
STXBP1 mutation (de novo)	Complex I	25418441
Zellweger syndrome	Complexes II+III, COX	25287621; 28753922

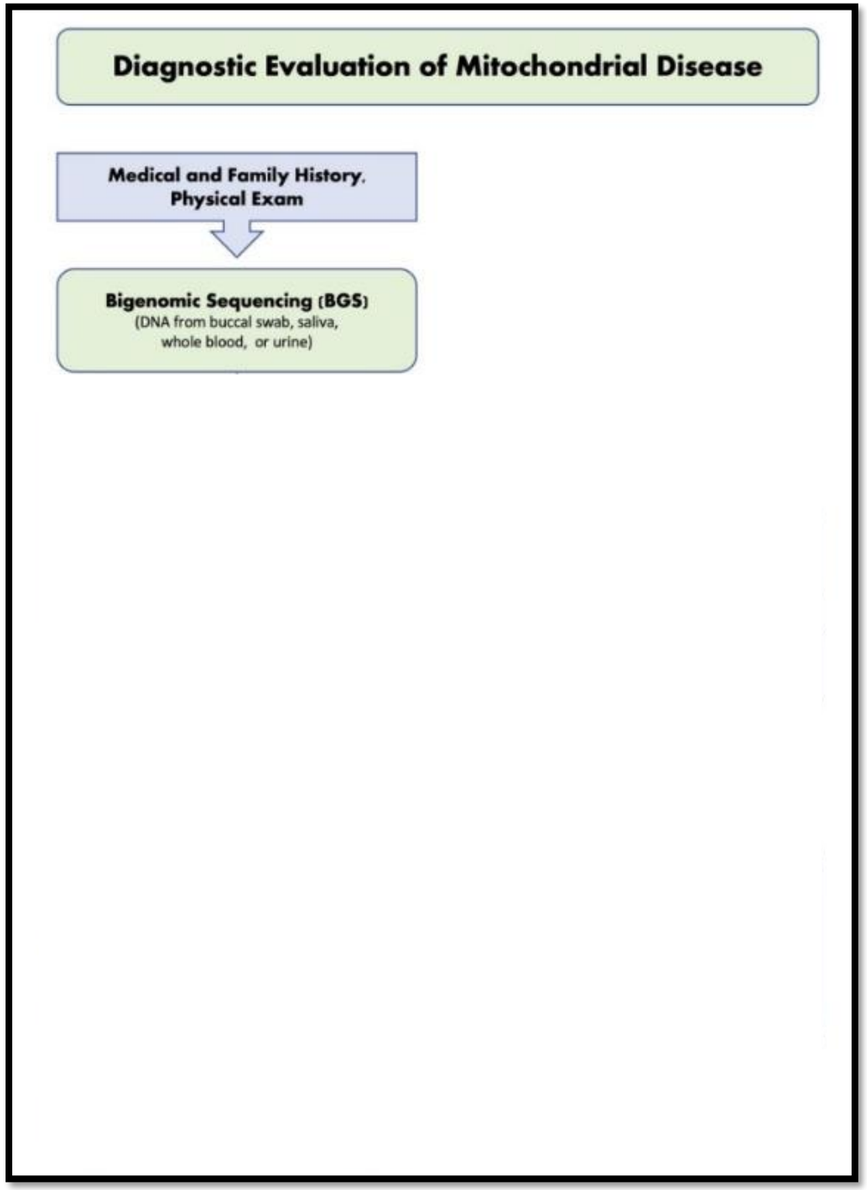
Parikh S et al. J Med Genet 2019;56:123–130

Primary Mitochondrial Disease

Primary mitochondrial disease = Mitochondrial disease

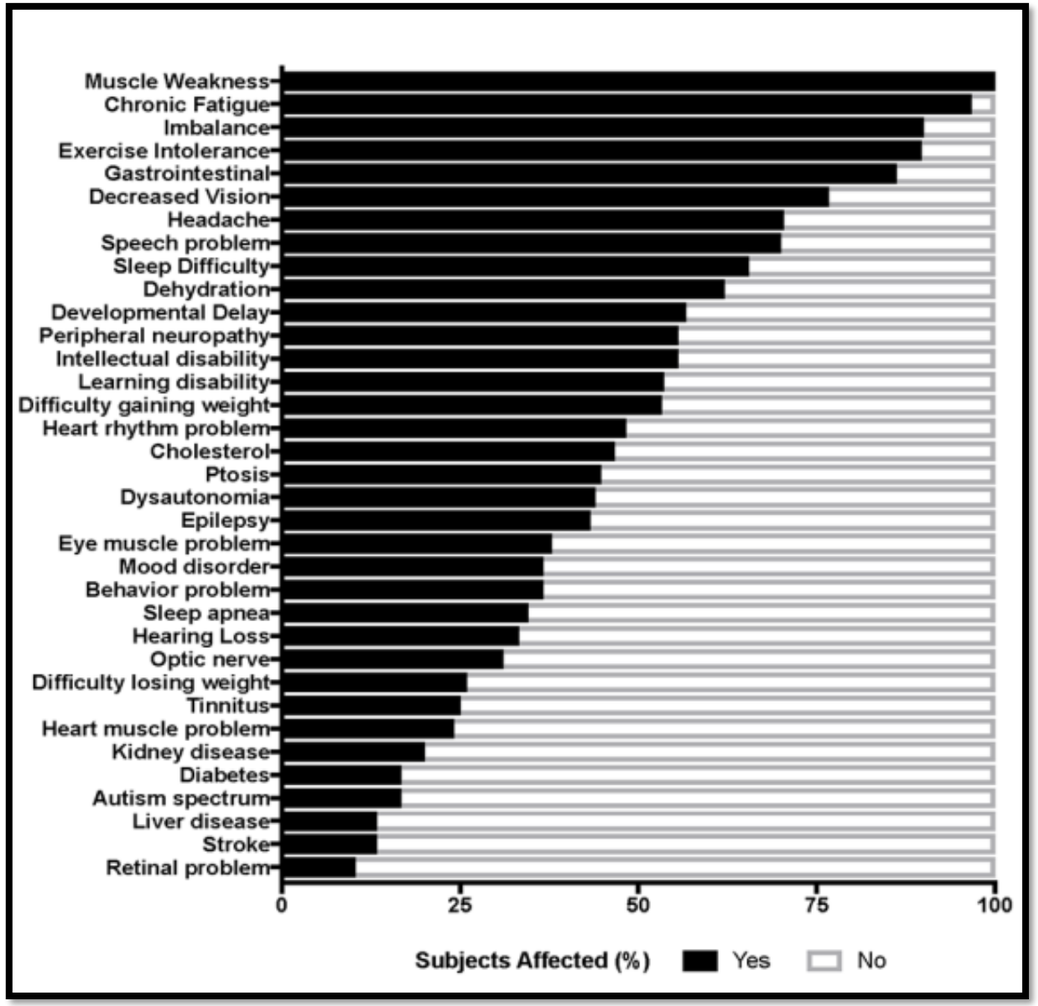
Secondary Mitochondrial dysfunction = Mitochondrial dysfunction

Primary Mitochondrial Disease



https://member.myhealthtoolkitla.com

Primary Mitochondrial Disease



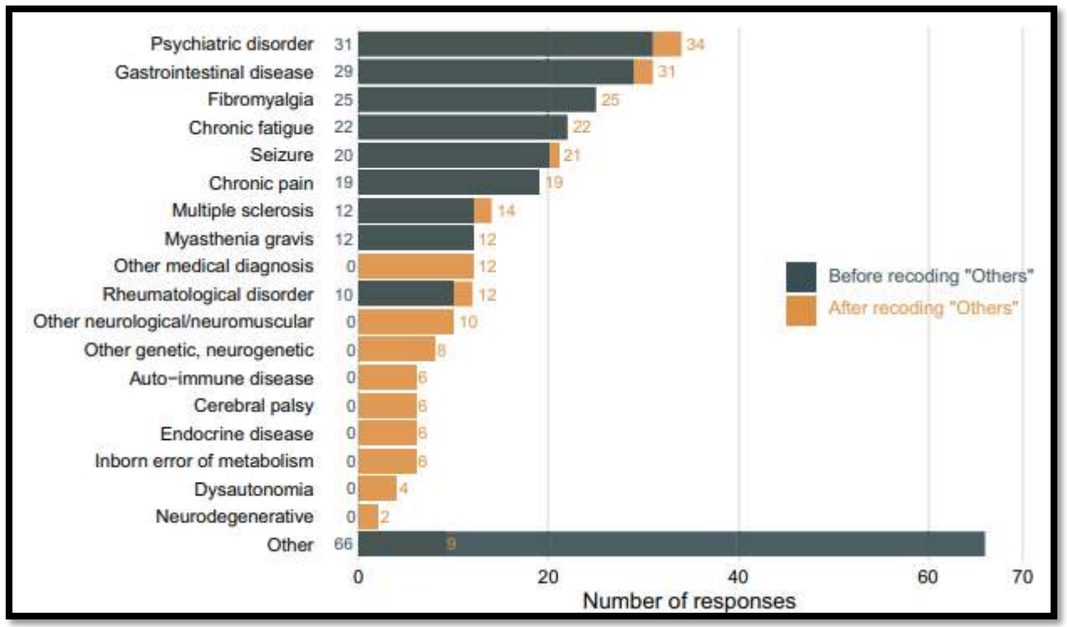
PLOS ONE | https://doi.org/10.1371/journal.pone.0197513

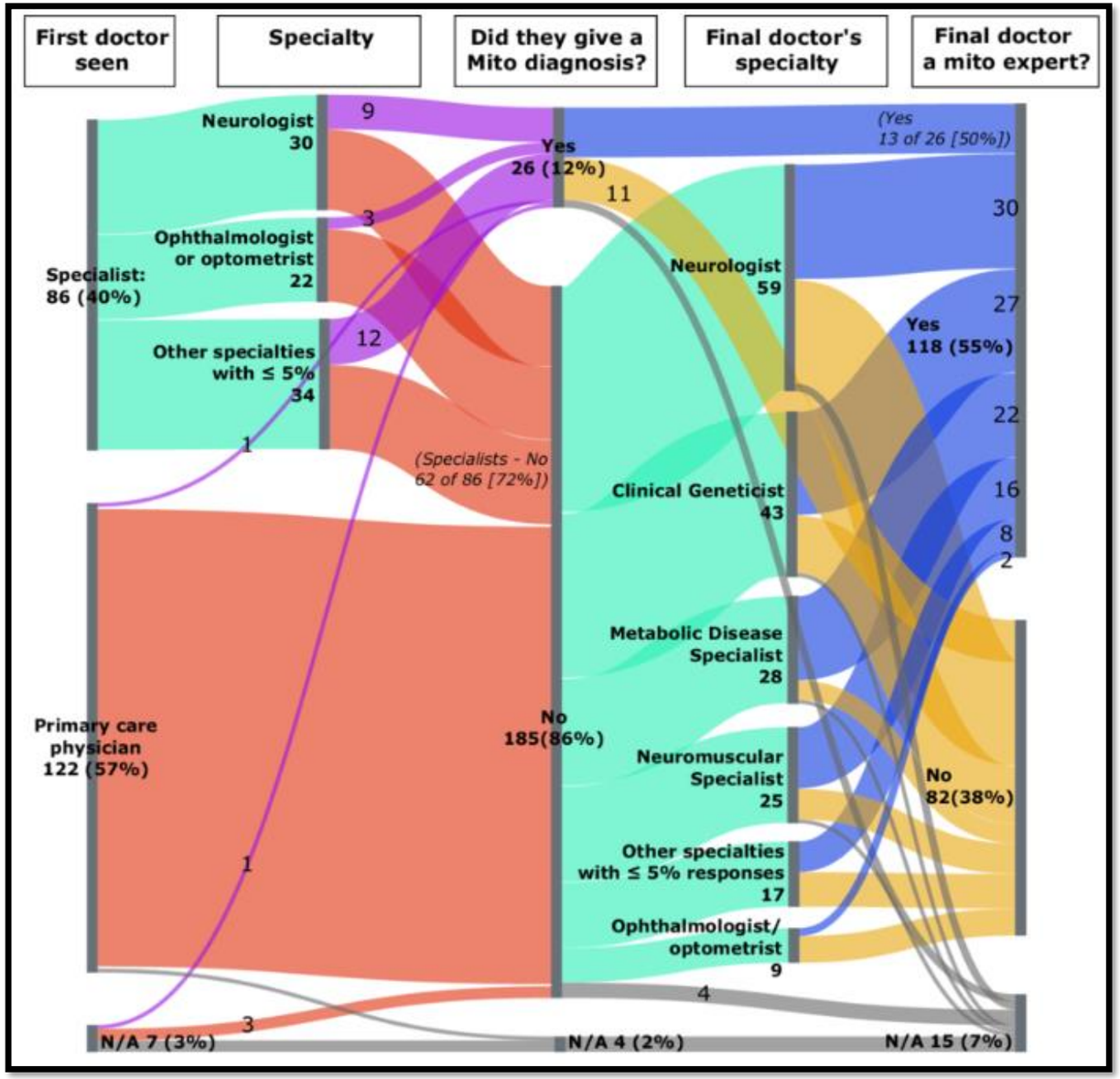
Most frequent patients/parents reported symptoms.*

Constitutional		Musculoskeletal		Neurological		Gastro-Intestinal		Cardiac		Other	
High frequency symptoms (in >50% of patients)											
Chronic fatigue	61%			Weakness	50%						
Medium frequency symptoms (in 25-50%of patients)											
Temperature instability	48%	Myalgia	38%	Ptosis	30%	Irritable bowel syndrome	33%			Anxiety	25%
				Headaches/Migraines	28%						
Exercise intolerance	42.5%			Developmental delay /Intellectual disability	27%	Dysphagia	25%				
Low frequency symptoms (in <25%of patients)											
Difficulty gaining weight	12%	Myoglobinuria	1.5%	Myoclonus	20%	Gastroparesis	23%	Arrhythmias	18%	Depression	19%
		Rhabdomyolysis	2%	PEO	17%	GI dysmotility	14%	SOB	11%	Thyroid disease	9%
Growth delay	6%			Seizures	17%	Nausea/vomiting	12%	Syncope	6%	Diabetes	7%
Cachexia	5%			Ataxia	17%	Pseudoobstruction	5%	Cardiomyopathy	4%	Short stature	7%
Lipoma	3%			Neuropathy	17%	Steatosis	4.5%			Parathyroid disease	7%
				Hypotonia	15%	Pancreatic dysfunction	3%			Hypogonadism	2%
				Spasticity	15%					Delayed puberty	3%
				Dysarthria	15%	Hepatopathy	2%			Renal tubulopathy	2%
				Optic atrophy	11%						
				Dystonia	10%						
				Hearing loss	9%						
				Stroke/TIA	7%						
				Developmental regression	5.5%						
				Autism	8%						
				Dementia	3.7%						

A. Karaa et al. / Molecular Genetics and Metabolism 119 (2016) 100–108

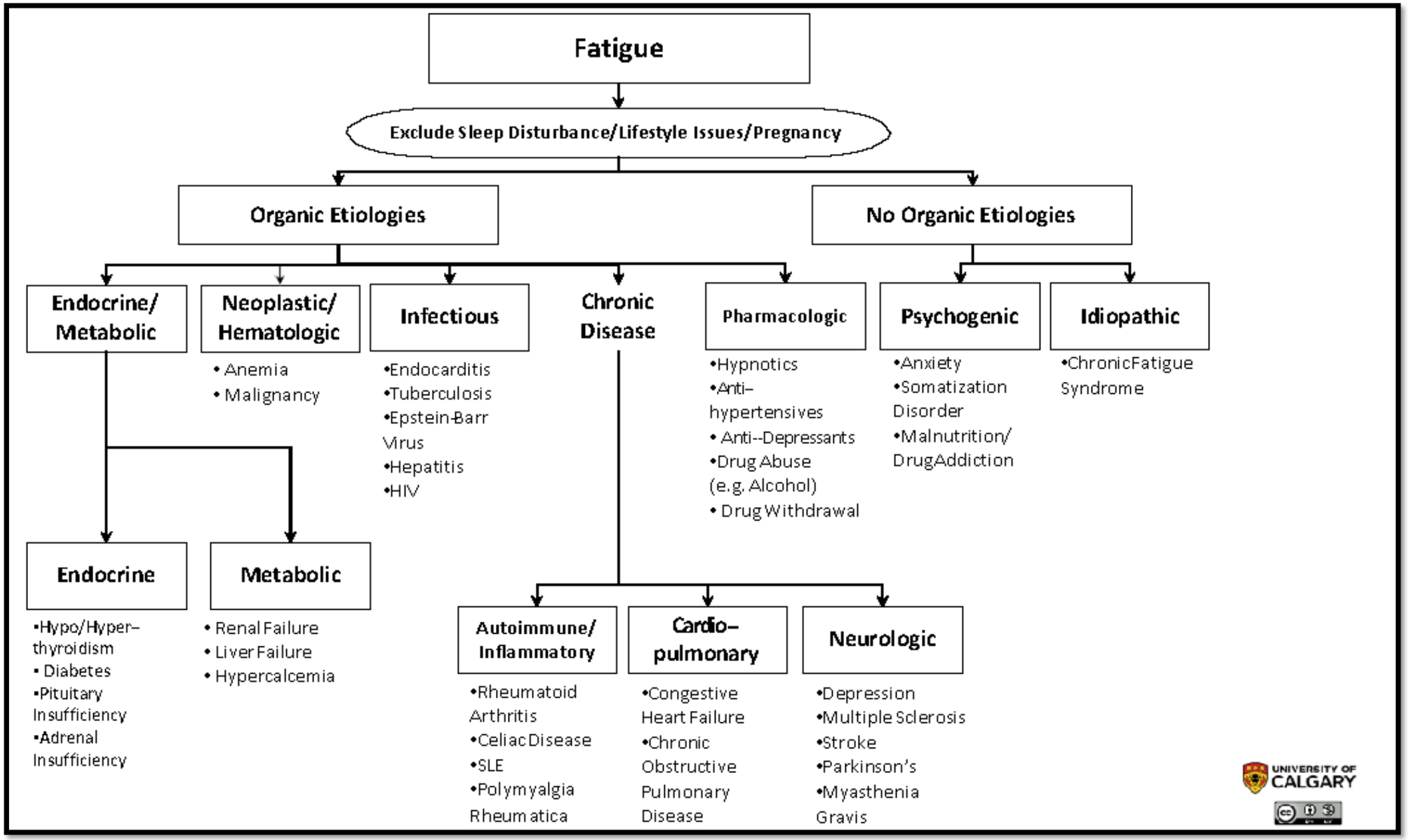
Primary Mitochondrial Disease



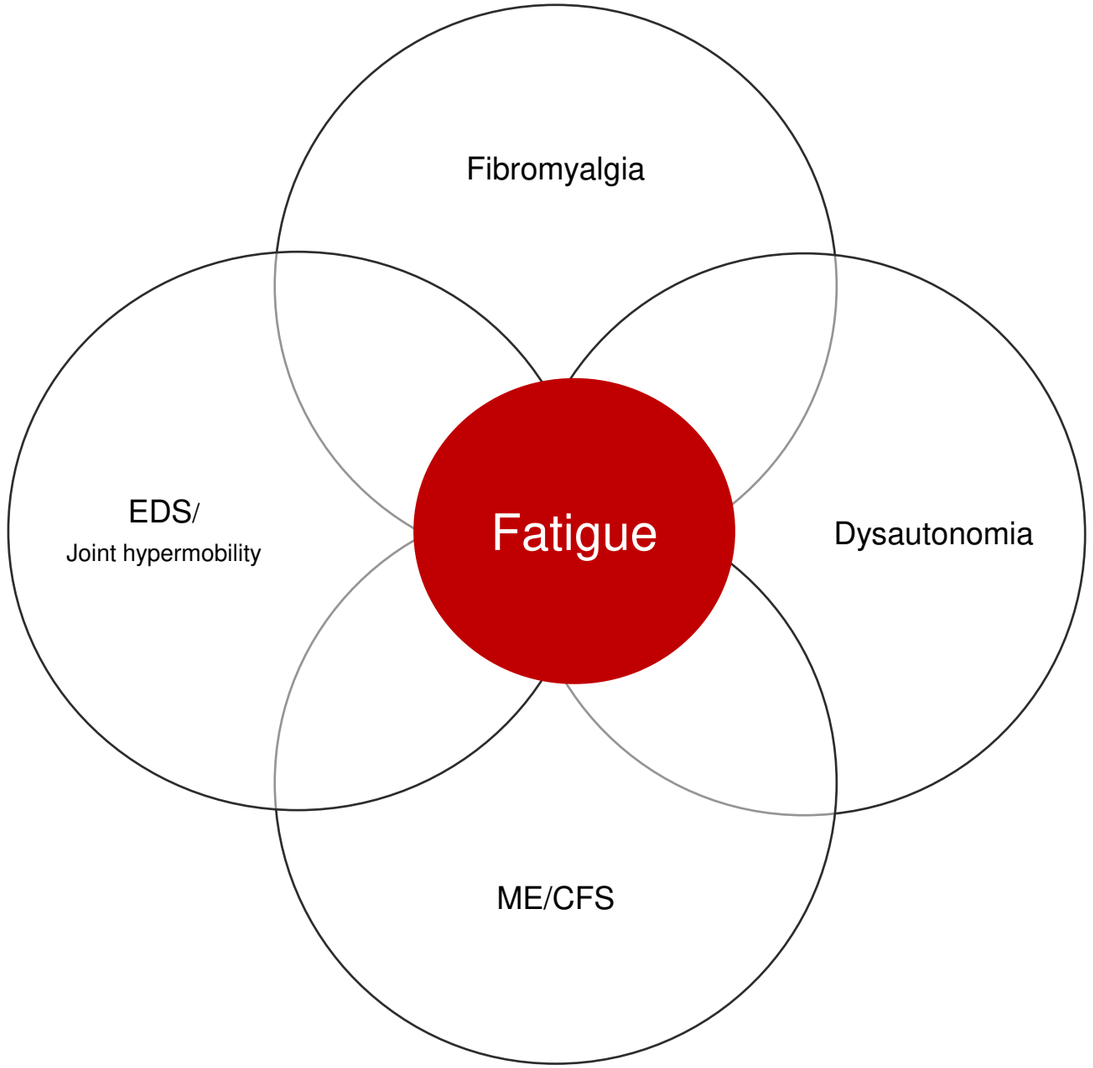


Thompson et al. Orphanet Journal of Rare Diseases (2023) 18:157

Primary or secondary Mito?



Primary or secondary Mito?

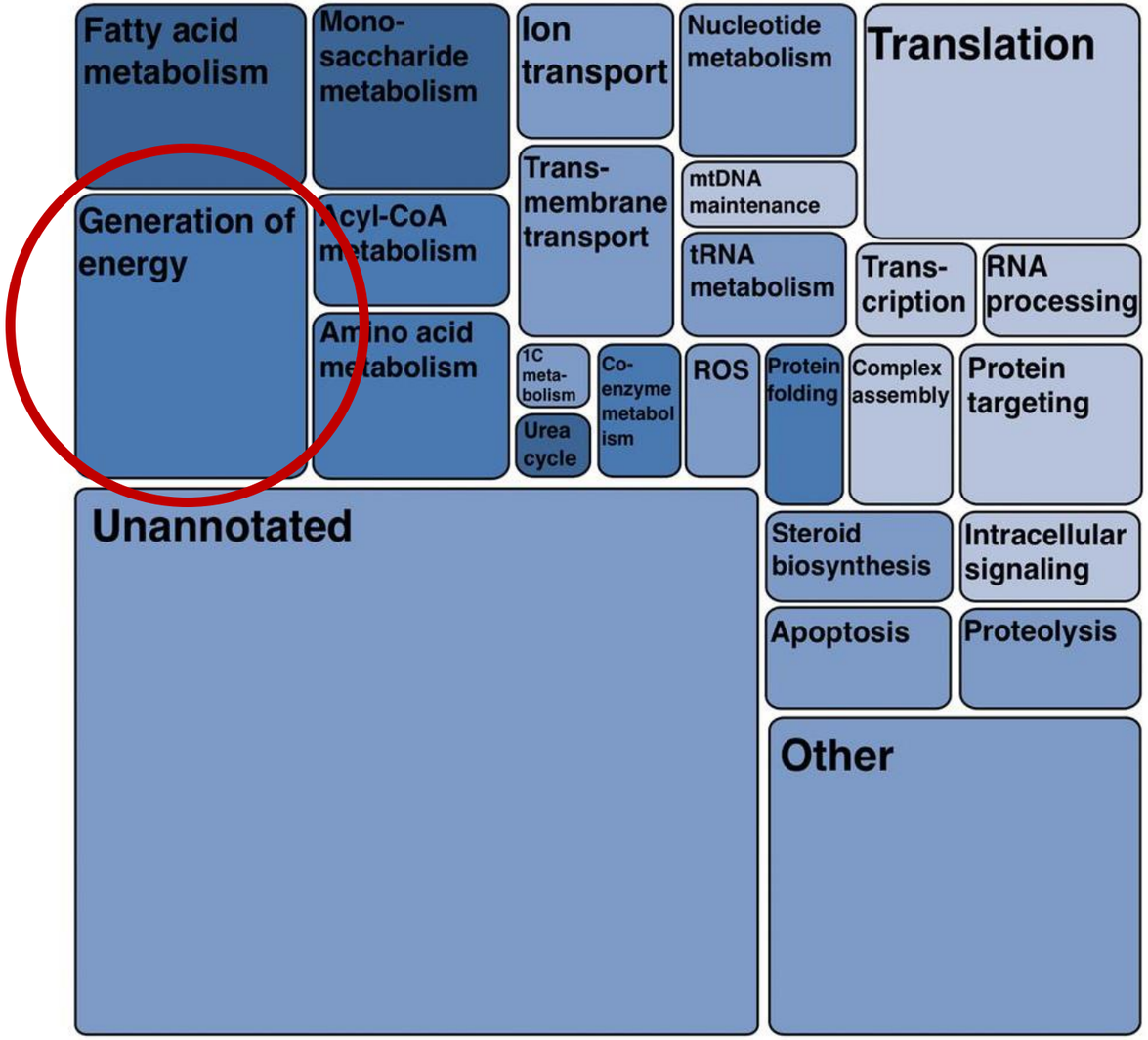


- Mitochondrial cytopathy
- Sick building syndrome
- Candida infection
- Multiple chemical sensitivities
- Dental amalgam disease
- MTHFR
- Heavy metal toxicity
- Mast cell activation disorder
- Chronic pain
- Small fiber polyneuropathy
- …..

Primary or secondary Mito?

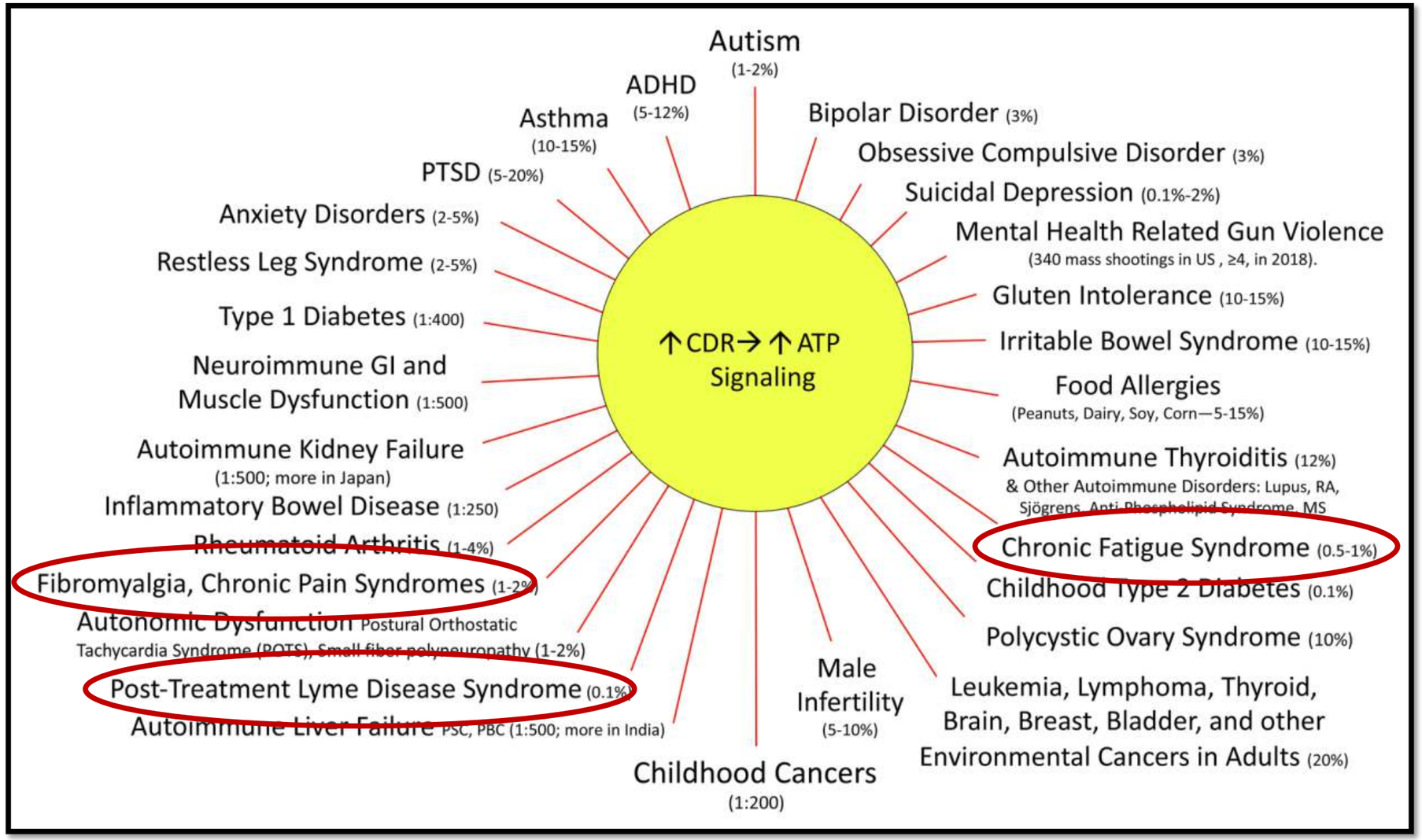
Mitochondria: Energy & Metabolism
ATP is an energy molecule → animates life

Primary or secondary Mito?



Essays In Biochemistry May 25, 2012,5223-35

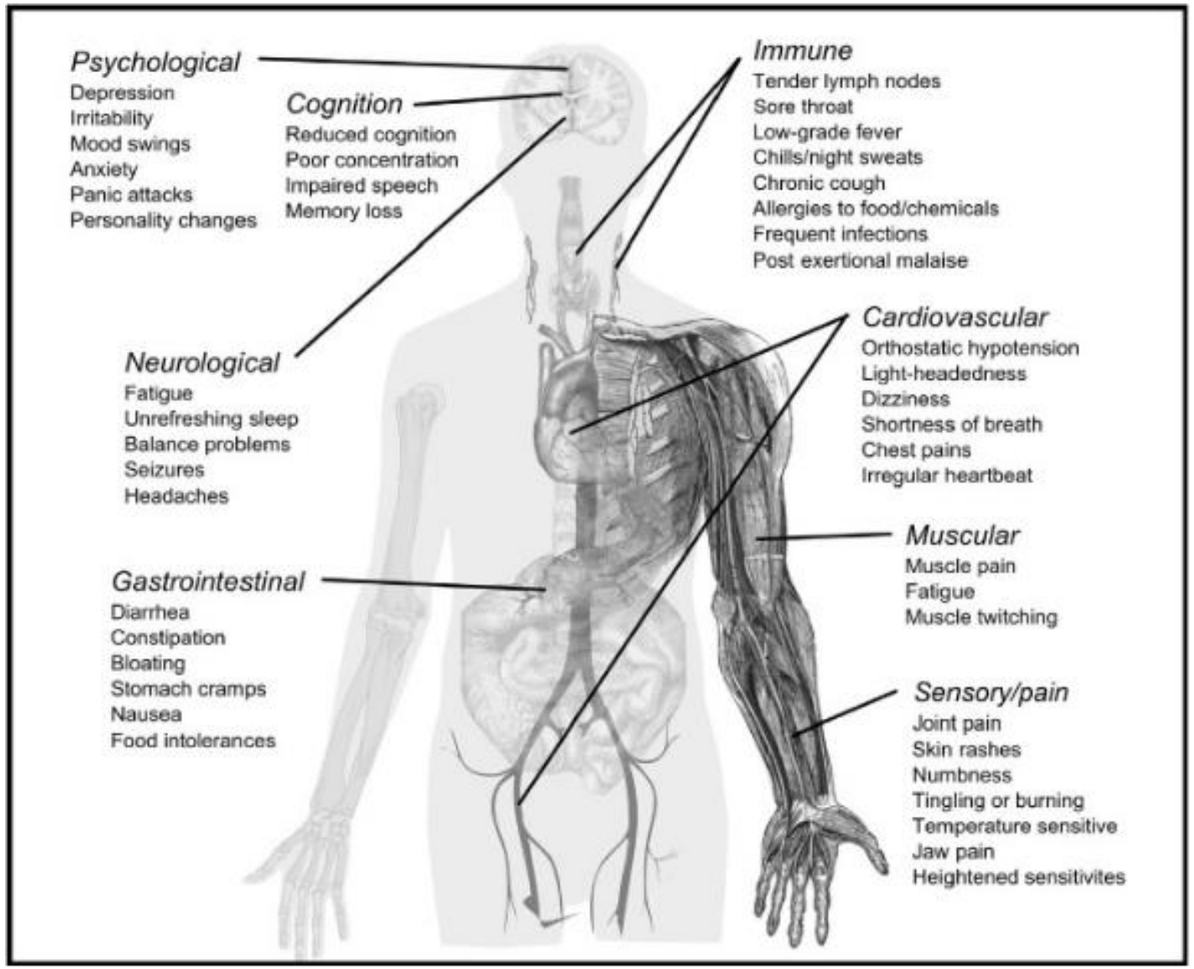
Primary or secondary Mito?



RK Naviaux, Mitochondrion 51 (2020) 40-55.

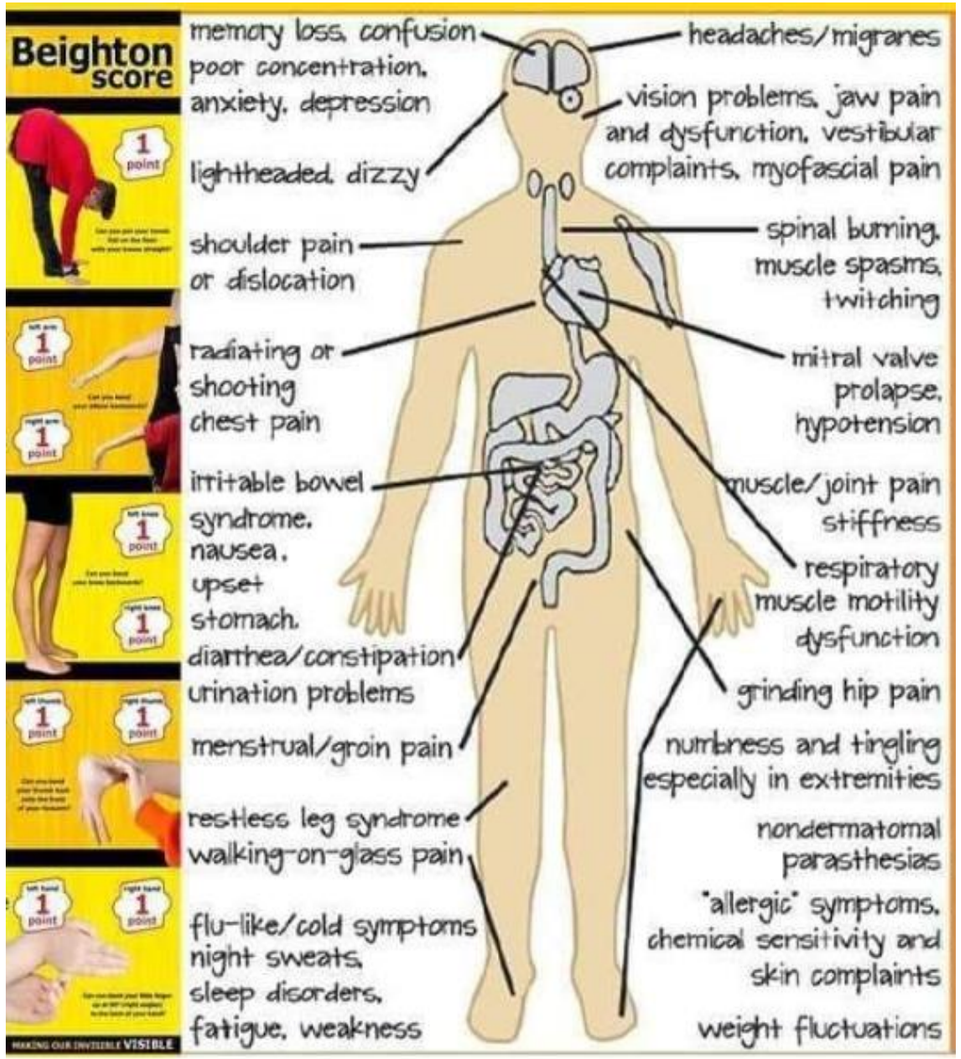
Primary or secondary Mito?

Chronic Fatigue syndrome



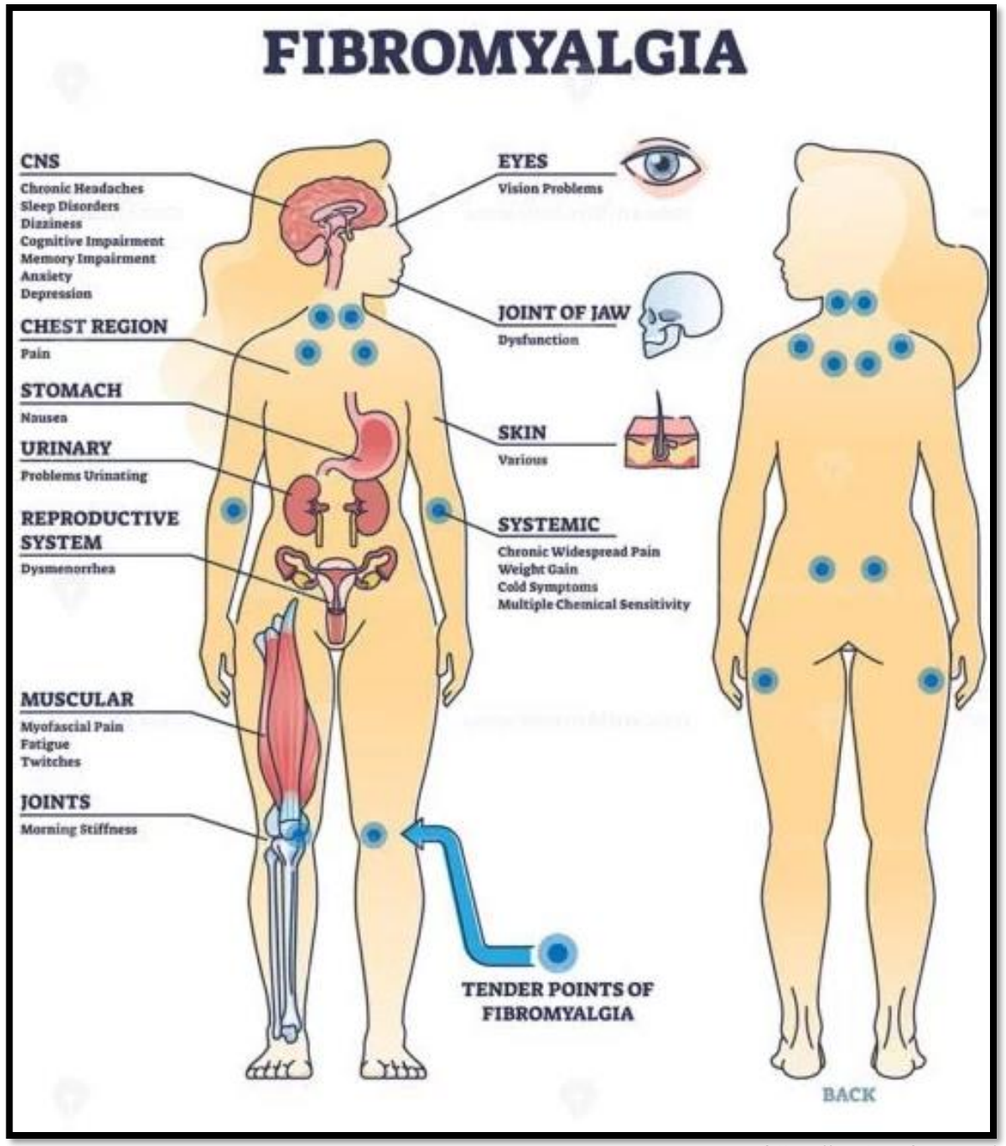
Armstrong et al. Metabolism in chronic fatigue syndrome. Adv Clin Chem. 2014;66:121–172

Ehlers Danlos Hypermobility



https://balanced-bodies.net/

Primary or secondary Mito?



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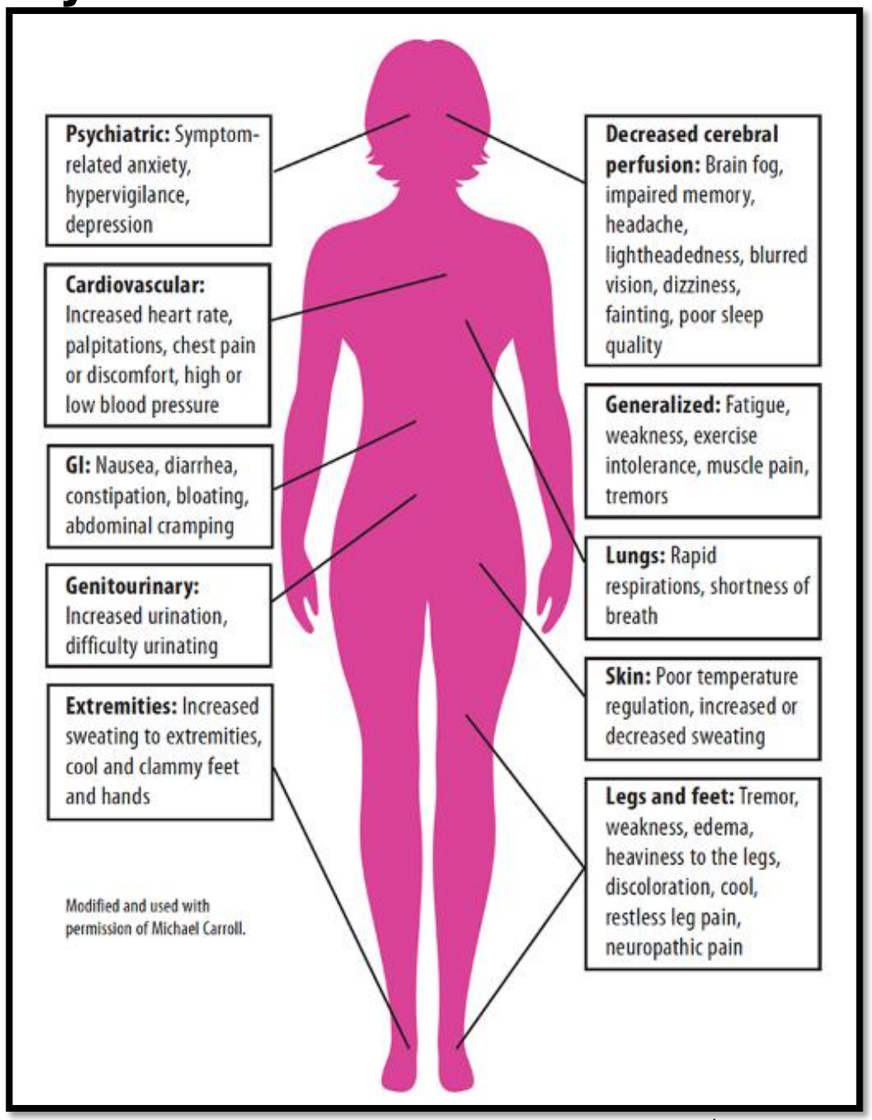
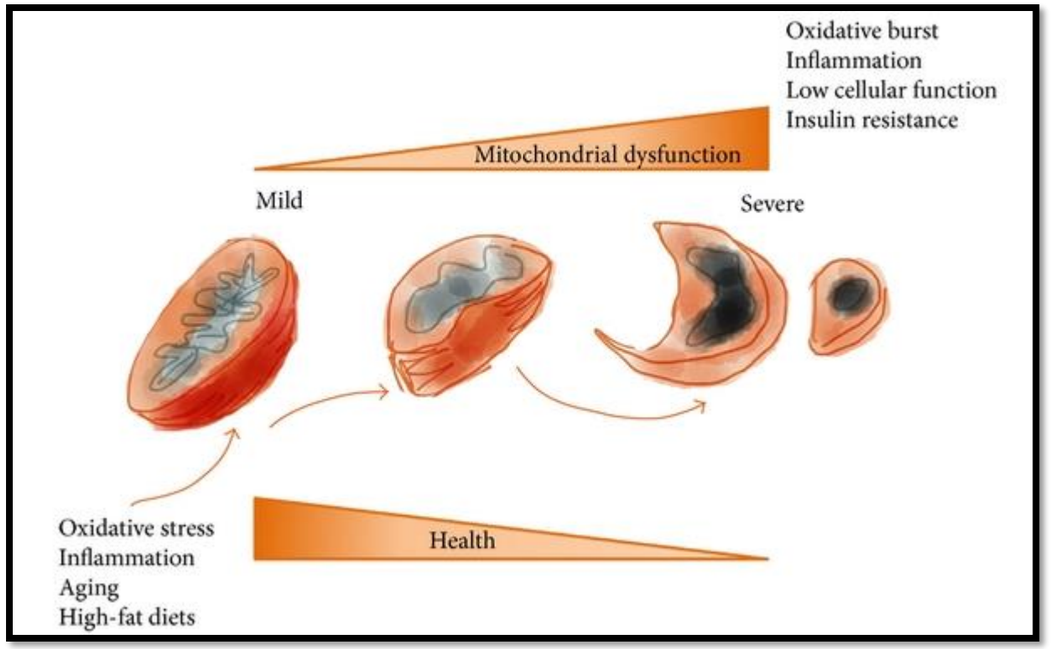
Dysautonomia/POTS

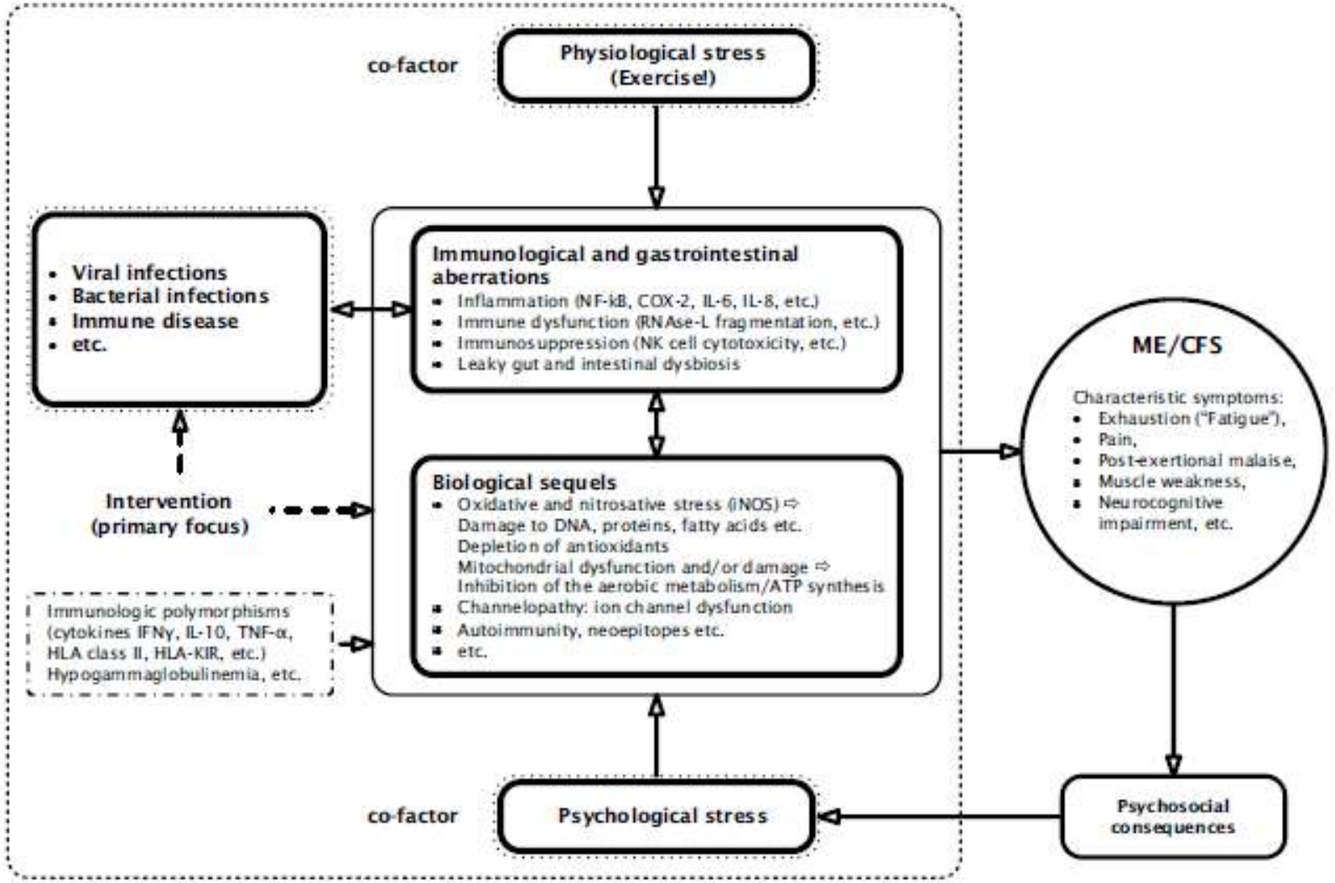


www.myamericannurse.com

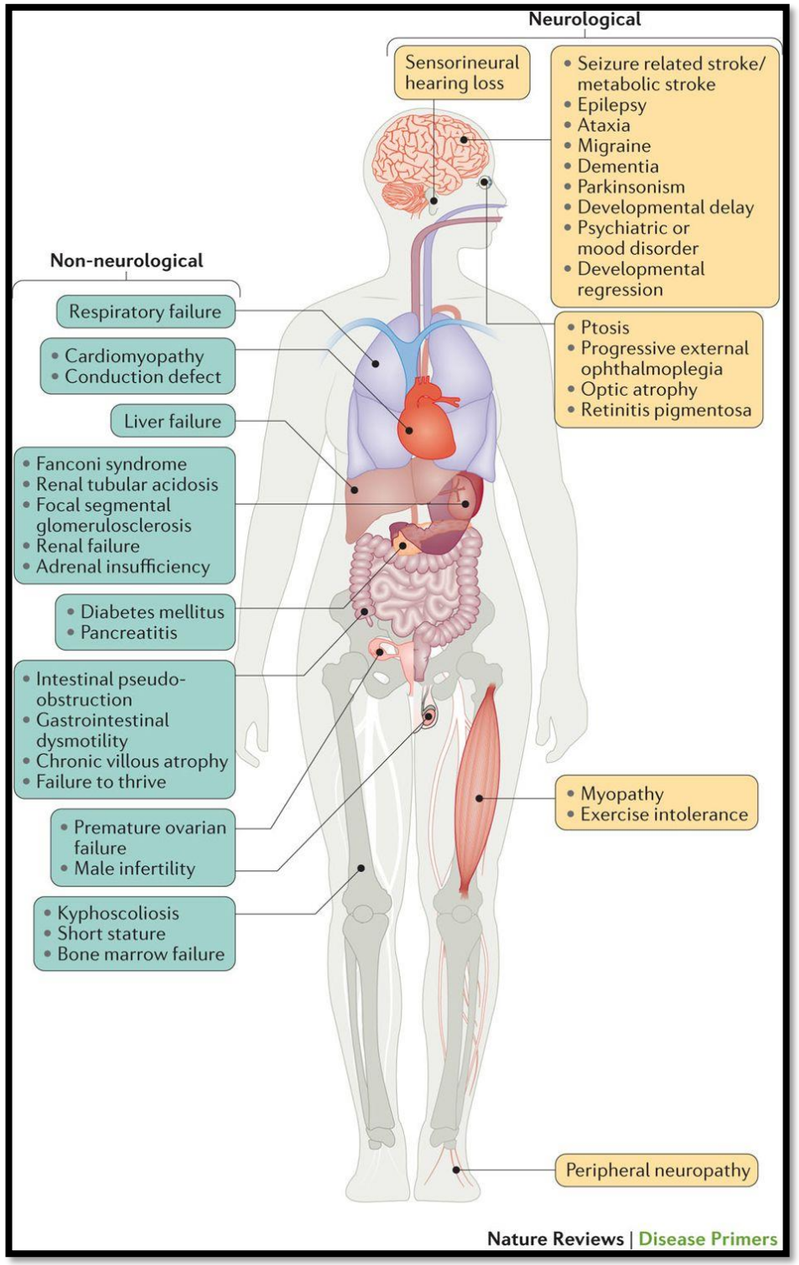
Primary or secondary Mito?

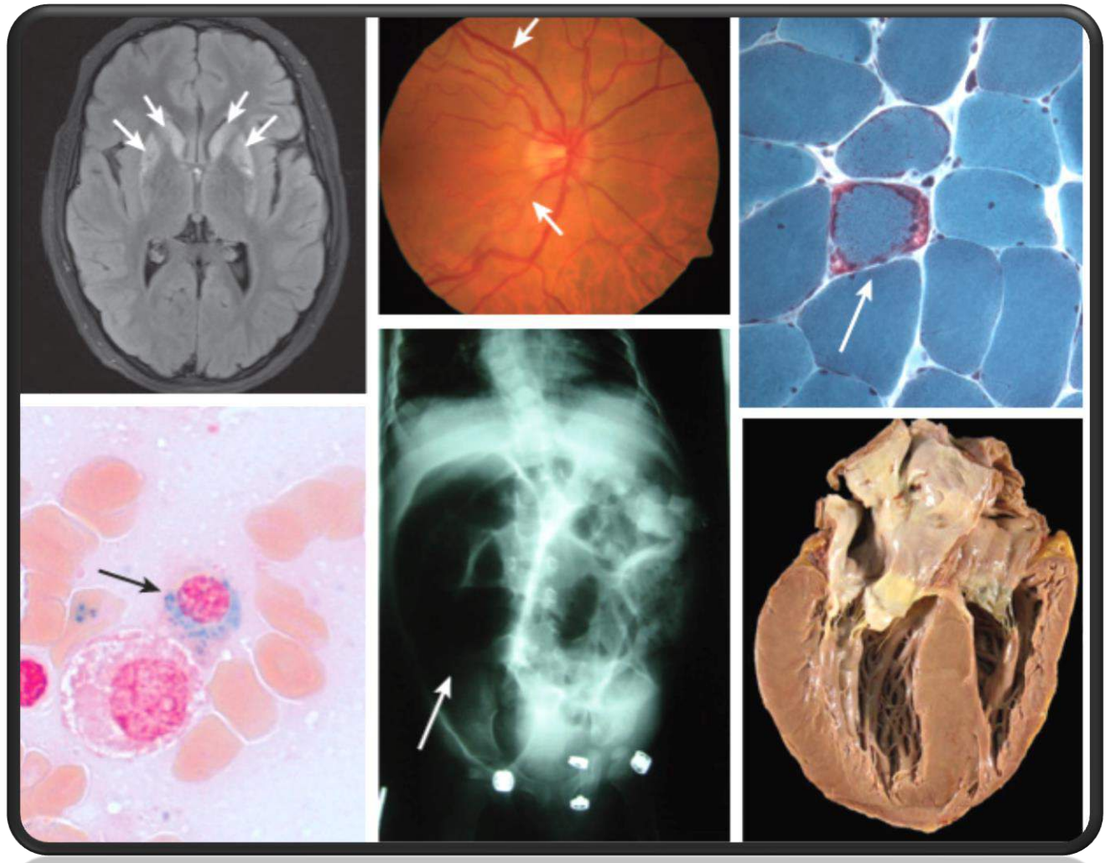


Mediators of Inflammation Volume 2013, Article ID 135698



Maes and Twisk *BMC Medicine* 2010, **8**:35





Vafai and Mootha, Nature 2012

Mitochondrial disorders are one of the most complex and heterogeneous group of diseases

Primary or secondary Mito?

Mitochondrial genetics

REVIEW

Diagnosis of 'possible' mitochondrial disease: an existential crisis

Sumit Parikh,[1] Amel Karaa,[2] Amy Goldstein,[3,4] Enrico Silvio Bertini,[5] Patrick F Chinnery,[6] John Christodoulou,[7,8] Bruce H Cohen,[9,10] Ryan L Davis,[11,12] Marni J Falk,[3,4] Carl Fratter,[13,14] Rita Horvath,[15,16] Mary Kay Koenig,[17] Michaelangelo Mancuso,[18] Shana McCormack,[3,4] Elizabeth M McCormick,[3] Robert McFarland,[19] Victoria Nesbitt,[19,20] Manuel Schiff,[21] Hannah Steele,[15,22] Silvia Stockler,[23] Carolyn Sue,[11,12,24] Mark Tarnopolsky,[25] David R Thorburn,[26,27,28] Jerry Vockley,[29] Shamima Rahman[30,31]

Parikh S, Karaa A, et al. J Med Genet. 2019 Mar;56(3):123-130.

Mitochondrial Medicine Society: www.mitosoc.org

Primary or secondary Mito?

Box 2 Potential harms arising from a diagnosis of 'possible' mitochondrial disease

- Ending diagnostic odyssey prematurely.
- Missing potentially treatable disorders.
- Psychological burden of mitochondrial disease diagnosis: parent/patient fear of progressive or degenerative disorder.
- Inaccurate recurrence risk counselling.
- Inappropriate preventative care.
- Unnecessary medical interventions at times of catabolic stress.
- Avoidance of needed medications owing to fear of mitochondrial toxicity.
- Inappropriate reproductive decisions taken.

Parikh S, Karaa A, et al. J Med Genet. 2019 Mar;56(3):123-130.

Primary or secondary Mito?

→ Recognizable syndrome?

Mitochondrial Disease Syndromes
Leigh syndrome
Alpers Syndrome
Lethal infantile mitochondrial disease
Pearson’s syndrome
Barth syndrome
Kearns-Sayre syndrome
Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)
Myoclonic epilepsy with ragged-red-fibers (MERRF)
Neuropathy, ataxia and retinitis pigmentosa (NARP)
Mitochondrial neuro-gastro-intestinal encephalomyopathy (MNGIE)
Leber’s hereditary optic neuropathy (LHON)
Chronic Progressive external ophthalmoplegia (CPEO)
Ataxia, neuropathy syndrome (ANS)

Primary or secondary Mito?

→ Recognizable syndrome? Red flags?

TABLE 1 Red-Flag Findings in Mitochondrial Disease

- Neurologic
  - Cerebral stroke-like lesions in a nonvascular pattern
  - Basal ganglia disease
  - Encephalopathy: recurrent or with low/moderate dosing of valproate
  - Neurodegeneration
  - Epilepsia partialis continua
  - Myoclonus
  - Ataxia
  - MRI findings consistent with Leigh disease
  - Characteristic MRS peaks
    - Lactate peak at 1.3 ppm TE (time to echo) at 35 and 135
    - Succinate peak at 2.4 ppm
- Cardiovascular
  - Hypertrophic cardiomyopathy with rhythm disturbance
  - Unexplained heart block in a child
  - Cardiomyopathy with lactic acidosis (>5 mM)
  - Dilated cardiomyopathy with muscle weakness
  - Wolff-Parkinson-White arrhythmia
- Ophthalmologic
  - Retinal degeneration with signs of night blindness, color-vision deficits, decreased visual acuity, or pigmentary retinopathy
  - Ophthalmoplegia/paresis
  - Fluctuating, dysconjugate eye movements
  - Ptosis
  - Sudden- or insidious-onset optic neuropathy/atrophy
- Gastroenterologic
  - Unexplained or valproate-induced liver failure
  - Severe dysmotility
  - Pseudo-obstructive episodes

http://www.mitosoc.org/toolkit

Primary or secondary Mito?

- Tissue pathology (RRF, COX, SDH…)
- Functional assays (ETC, skin biopsy, …)
- Biochemical tests (lactate, organic acids…)

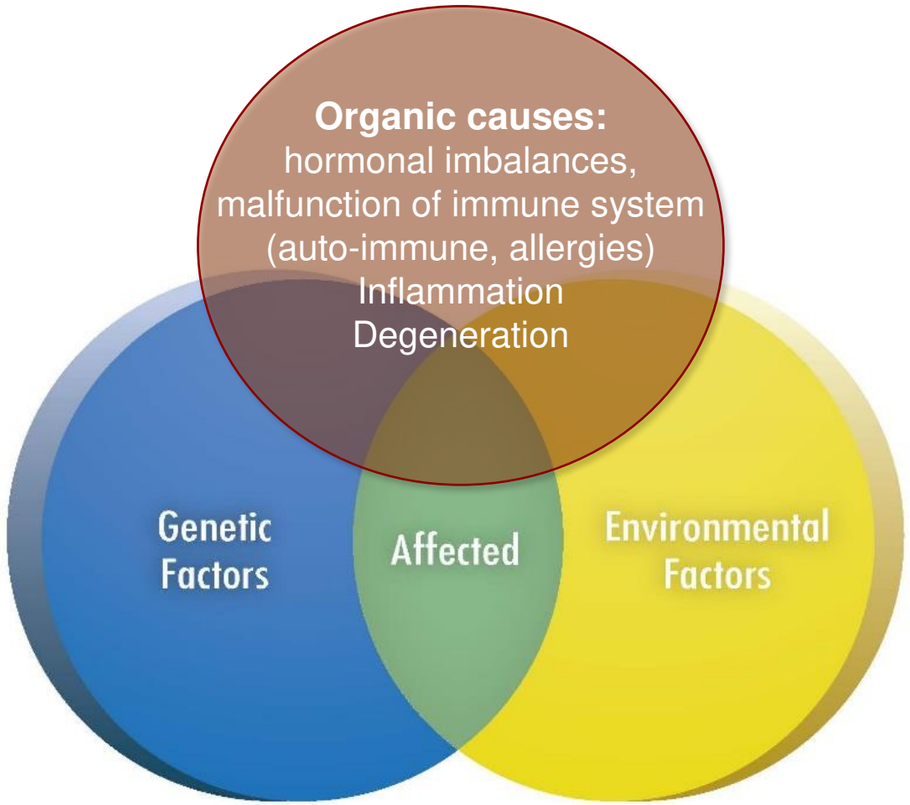
Current Limitations of biochemical testing

- Imperfect sensitivity and specificity.
- Secondary mitochondrial dysfunction leading to abnormal results.
- Interlab variability of methods and reference ranges.
- Challenges with tissue processing.

Parikh S, Karaa A, et al. J Med Genet. 2019 Mar;56(3):123-130.

Primary or secondary Mito?

- Non-Mendelian disorders
- Other Mendelian disorders to be identified
- Multifactorial etiologies



https://www.mitonetwork.org/about

MITOCHONDRIAL CARE NETWORK

ABOUT CENTERS NEWS CONTACT

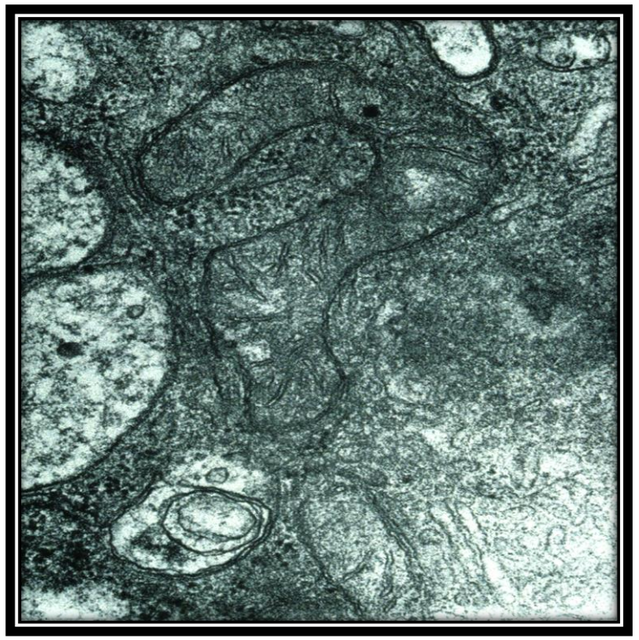
What is the Mitochondrial Care Network (MCN)?

The MCN represents a group of physicians at medical centers across the country that have expertise and experience in providing coordinated, multidisciplinary care for patients with genetic mitochondrial disease. A complete list of MCN Centers can be found here.

The effort is a collaboration between mitochondrial physicians in the Mitochondrial Medicine Society and US based patient advocacy groups (Foundation for Mitochondrial Medicine, MitoAction, United Mitochondrial Disease Foundation).

MMS Papers *(links to journal articles open in a new window*

Thank you, and any questions?



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