

Mitochondrial Disorders

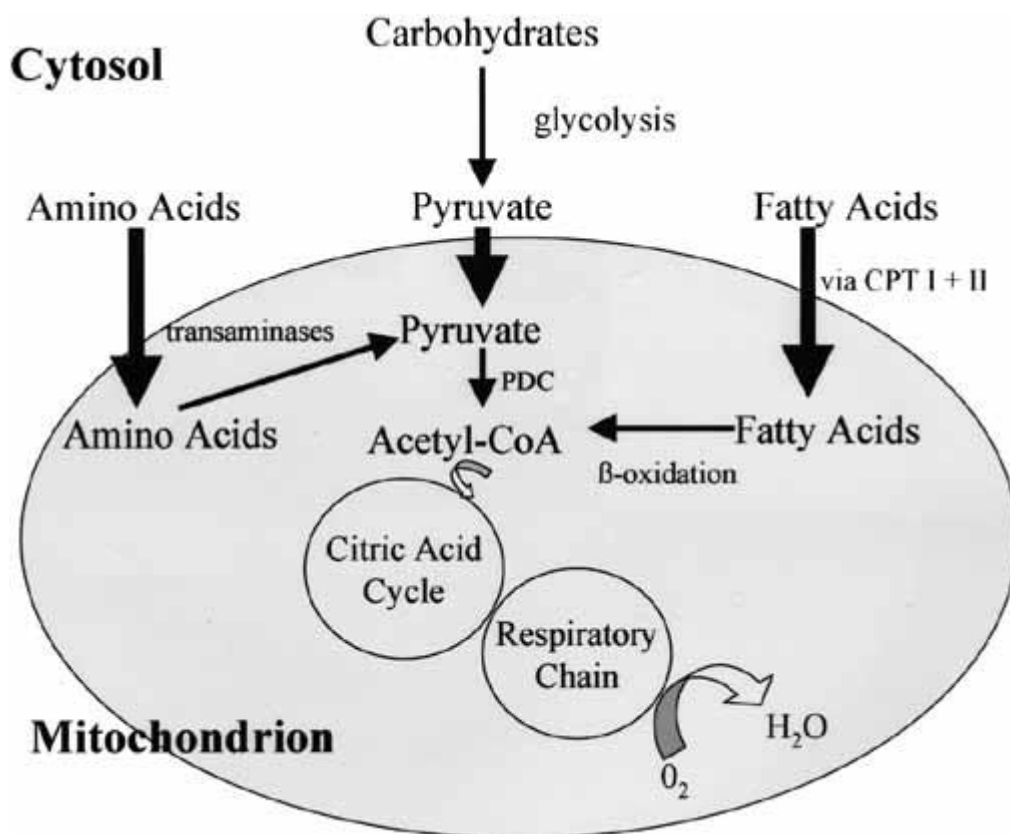


Figure 1. The biochemistry of mitochondrial energy production.

Table 1. Biochemical classification of mitochondrial diseases.

Defects of mitochondrial substrate transport

- Camitine deficiency (primary muscle, primary systemic, secondary)
- Camitine palmitoyltransferase (CPT) deficiencies
 - CPT I deficiency, hepatic form
 - CPT II deficiency, muscular and fatal infantile forms
- Camitine-acylcarnitine translocase deficiency

Defects of mitochondrial substrate utilization

Fatty acid oxidation

- Defects in very long chain, long chain, medium chain and short chain acyl-CoA dehydrogenases (VLCAD, LCAD, MCAD, SCAD)
- Electron transfer flavoprotein (ETF) deficiency
- Trifunctional enzyme deficiency
- 2,4-Dienoly-CoA reductase deficiency
- Short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
- Riboflavin-responsive multiple beta-oxidation enzyme defects

Ketone synthesis

- 3-Hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase deficiency

Pyruvate oxidation

- Deficiency of pyruvate dehydrogenase complex components
 - Pyruvate dehydrogenase (E₁) deficiency
 - Dihydrolipoamide acetyl transferase (E₂) deficiency
 - Dihydrolipoamide dehydrogenase (E₃) deficiency
 - Protein X deficiency
 - Phospho-E phosphatase deficiency

Defects of the citric acid cycle

- Alpha-ketoglutarate dehydrogenase complex deficiency
- Fumarase deficiency
- Aconitase deficiency

Defects of the respiratory chain

- Complex I (NADH-ubiquinone reductase) deficiency
- Complex II (succinate-ubiquinone reductase) deficiency
- Coenzyme Q₁₀ deficiency
- Complex III (ubiquinol-cytochrome *c* reductase) deficiency
- Complex IV (cytochrome *c* oxidase) deficiency
- Multiple respiratory enzyme deficiencies

Defects of oxidation-phosphorylation coupling

- Complex V (ATP synthase) deficiency
- Luft's disease

Table 2. Genetic classification of mitochondrial diseases.

Defects of Mitochondrial DNA

- Point mutations (maternal inheritance)
- Large-scale rearrangements of mtDNA (usually sporadic)
 - Single deletions
 - Duplications

Defects of nuclear DNA (mendelian inheritance)

- Defects in genes encoding mitochondrial proteins (enzymes, translocases or structural proteins)
- Defects of mitochondrial protein importation
- Defects of intergenomic communication
 - Multiple deletions of mtDNA
 - Depletion of mtDNA

Table 3. The respiratory chain complexes.

Enzyme complex	No. of mtDNA-encoded subunits/total no. of subunits	mtDNA genes encoding subunits
I (NADH-ubiquinone reductase)	7/approx.40	ND1, 2, 3, 4, 4L, 5, 6
II (Succinate-ubiquinone reductase)	0/4	
III (Ubiquinol-cytochrome <i>c</i> reductase)	1/11	cytochrome <i>b</i>
IV (Cytochrome <i>c</i> oxidase)	3/13	COX I, COX II, COX III
V (ATP synthase)	2/14	ATPase 6, 8

Table 4. Defects in mtDNA causing syndromes with neuromuscular manifestations.

Phenotype	mtDNA defect		Inheritance (if known)	References
	Type of mutation	Gene		
Myopathy	Multiple deletions		Sporadic	92
	Single duplication			108
	mtDNA depletion		AR	29, 118, 120, 193
	A3243G, A3251G, C3303T	tRNA ^{Leu(UUR)}	Maternal	25, 78, 180
	A12320G	tRNA ^{Leu(CUN)}		203
	T14709C	tRNA ^{Glu}	Maternal	79
	C15990T	tRNA ^{Phe}	Sporadic	116
	A8344G	tRNA ^{Lys}		77, 173
	G9952A	Cox III	Sporadic	81
	Multiple point mutations + a microdeletion	Cytochrome <i>b</i>	Sporadic	1
+ Respiratory failure + Cardiomyopathy	A3243G, T3250C, A3302G	tRNA ^{Leu(UUR)}	Maternal	15, 73, 93
	C3254G, A3260G, C3303T	tRNA ^{Leu(UUR)}	Maternal	25, 95, 213
	A8344G	tRNA ^{Lys}		173
	A4317G	tRNA ^{Ile}		184
Myoglobinuria	Multiple deletions			139
	15-bp deletion	COX III	Sporadic	96
PEO (± other signs)	Single deletions		Sporadic/mat	86, 205
	Tandem duplication		Maternal	55
	Multiple deletions		AR/AD	18, 170, 217, 218
	A3243G, C3256T	tRNA ^{Leu(UUR)}	Sporadic/mat	78, 117
	A5692G, A5703G	tRNA ^{Asn}	Sporadic	117, 167
	T4285C, T4274C, G4298A	tRNA ^{Ile}		35, 175, 187
	A8344G	tRNA ^{Lys}	Maternal	77
KSS	T12311C, G12315A	tRNA ^{Leu(CUN)}		65, 83
	Single deletion		Sporadic	86, 205
	Tandem duplication		Sporadic	23
Encephalomyopathy	T8993G	ATPase 6	Sporadic	158
	A3243G, A3243T	tRNA ^{Leu(UUR)}	Maternal	78, 171
	T14709C	tRNA ^{Glu}	Maternal	79
	G15915A	tRNA ^{Thr}		134
MERRF	A8344G	tRNA ^{Lys}	Maternal	77
	Multiple deletions			16
	A8344G, T8356C, G8363A	tRNA ^{Lys}	Maternal	140, 172, 174, 214
MELAS	A3243G	tRNA ^{Leu(UUR)}	Maternal	78
	Single deletion		Sporadic	28
	A3243G, A3252G, T3271C, T3291C, A3260G	tRNA ^{Leu(UUR)}	Maternal	72, 78, 74, 133
	A583G	tRNA ^{Phe}	Sporadic	80
	G1642A	tRNA ^{Val}		189
	A5814G	tRNA ^{Cys}		106
	T3308C	ND1	Maternal	31
	A11084G	ND4		100
	G13513A	ND5		158
	T9957C	COX III	Maternal	107
	T8993G	ATPase 6	Maternal	197
	T8356C	tRNA ^{Lys}	Maternal	214
	T7512C	tRNA ^{Ser(UCN)}	Maternal	128
Leigh syndrome	A3243G	tRNA ^{Leu(UUR)}	Sporadic	30
	Single deletion		Sporadic	149
	5537 T insert	tRNA ^{Trp}	Maternal	159
	A8344G	tRNA ^{Lys}	Maternal	149
	A1644T	tRNA ^{Val}	Maternal	34
Polyneuropathy	T8993C, T8993G, T9176C	ATPase 6	Maternal	32, 149, 157
	Multiple deletions		AD/sporadic	33, 111, 114
	Single deletion			210
	A3243G	tRNA ^{Leu(UUR)}	Maternal	60, 82, 97, 155
	A8344G	tRNA ^{Lys}		36, 129
	G5549A	tRNA ^{Trp}		131

Table 4. Defects in mtDNA causing syndromes with neuromuscular manifestations (Continued).

Phenotype	mtDNA defect		Inheritance (if known)	References
	Type of mutation	Gene		
Sensory ataxic neuropathy	Multiple deletions		Sporadic	59
	A8344G	tRNA ^{Lys}	Maternal	26
MNGIE	Multiple deletions		AR/sporadic	84, 135, 196
	G8313A	tRNA ^{Lys}	Sporadic	202
NARP	T8993G	ATPase 6	Maternal	87, 160, 197
Motor neuron disease	5-bp microdeletion	COX I	Sporadic	42

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; Mat, maternal. Other abbreviations as defined in text.

Table 5. Central nervous system manifestations of mitochondrial diseases.

Strokelike episodes
Seizures
Myoclonus
Optic neuropathy
Sensorineural hearing loss
Ataxia
Developmental delay or regression
Dementia
Vascular headache
Myelopathy
Dystonia
Basal ganglia calcification
Elevated CSF protein concentration.

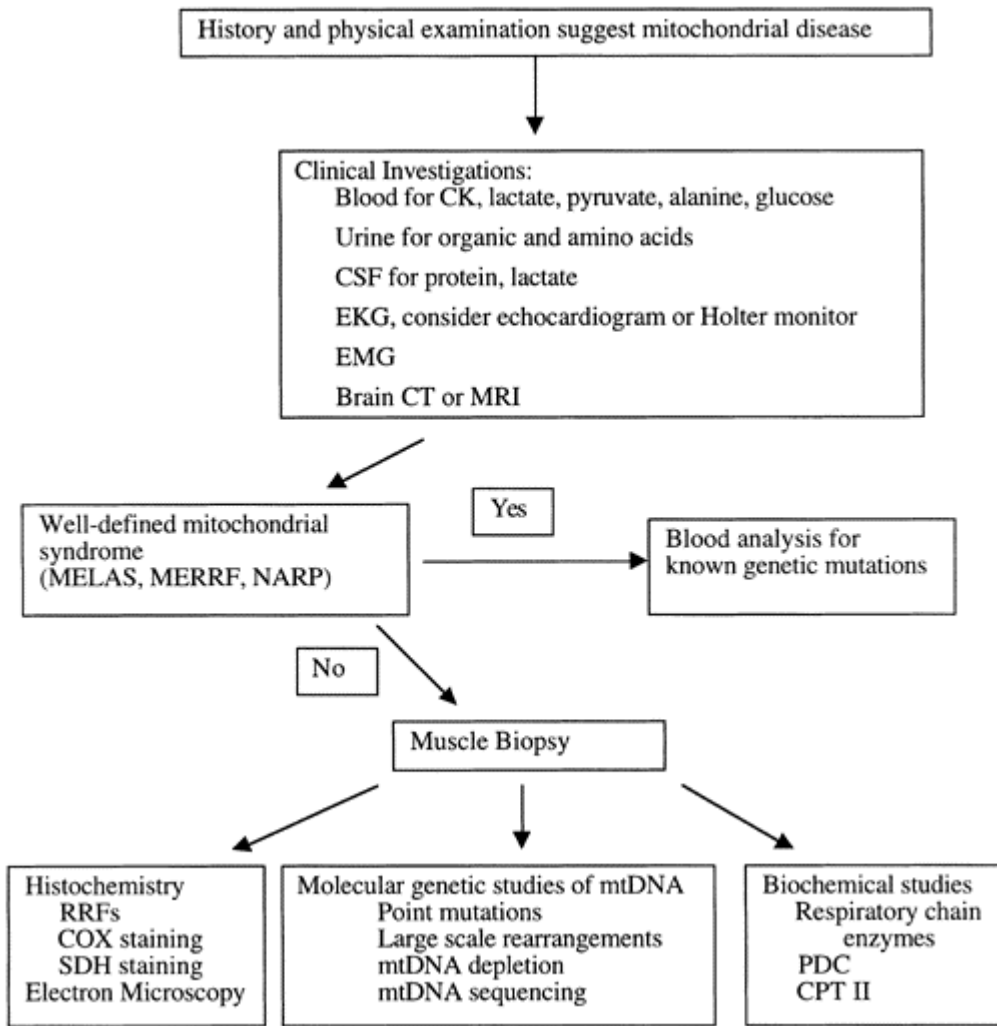


Figure 2. Diagnostic evaluation for patients with neuromuscular symptoms and suspected mitochondrial disease.