Mitochondrial Disorders
The New Frontier

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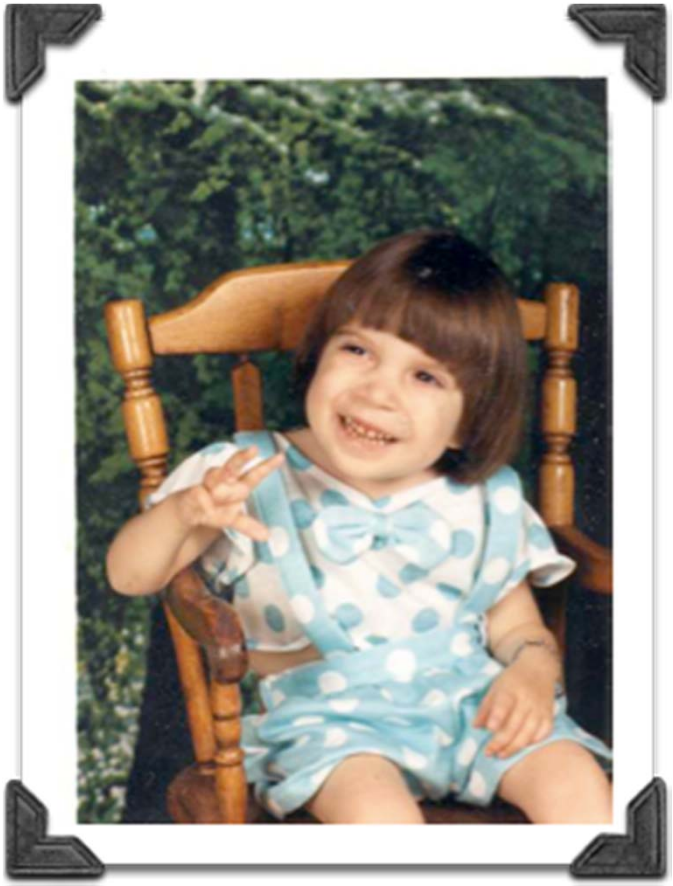
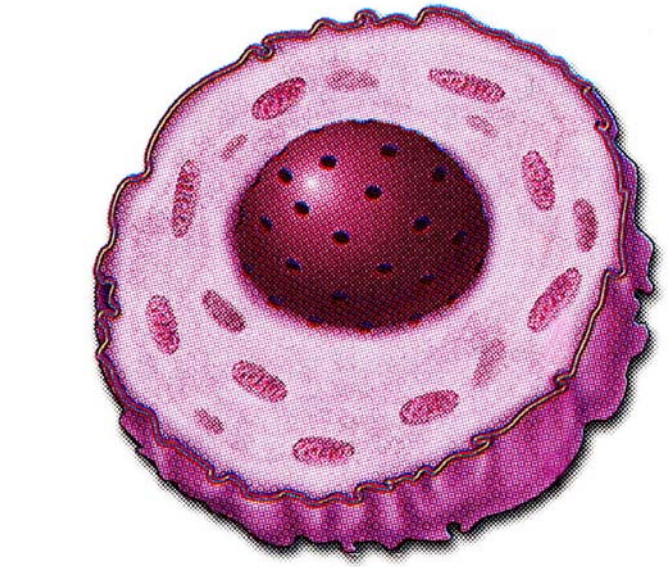
Conflicts of Interest

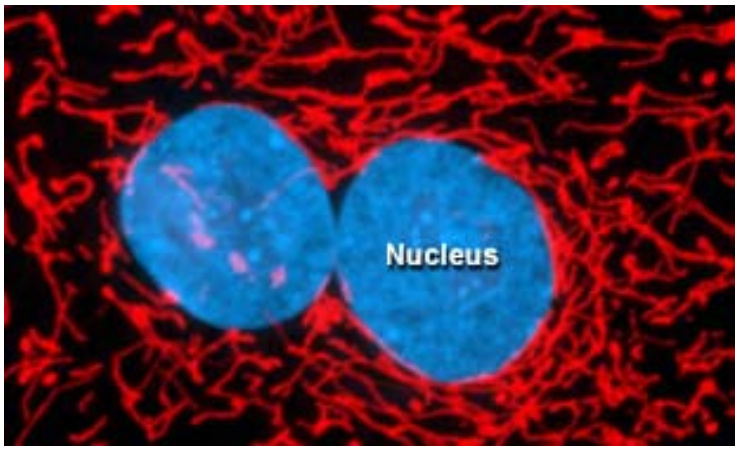


Diana
DOB 6/20/1982
DOD 9/4/1994

What Are Mitochondria?

- subcellular organelles
- 1 micron in length
  - cigar shaped (in vitro)
  - complex structure in vivo
- Comprised of ~1100 structural and enzymatic proteins
- Most of these proteins are encoded by nDNA
- 13 proteins of the ETC are encoded by mtDNA, resides in the mitochondria
  - ~16.5kB
  - 37 genes
    - 2rRNA
    - 22 tRNA
    - 13 structural proteins of the ETC





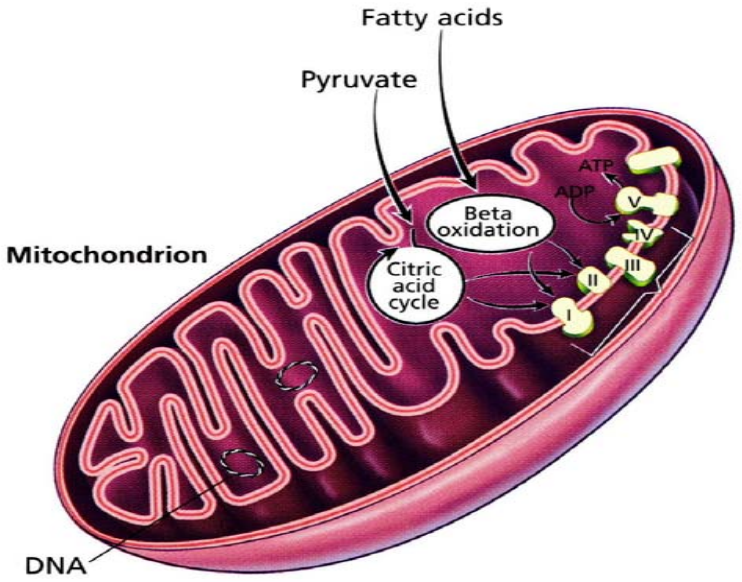
What do mitochondria do?

(1) generate ATP ☀

(2) critical component of apoptosis
✔ ➟ ✗

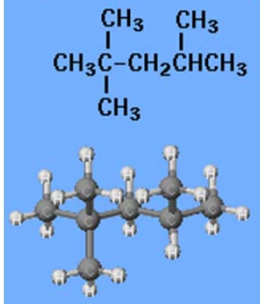
(3) generate free radicals 0_2 ➟ 0_2●

(4) Roles in most neurodegenerative diseases and some cancers ⌛



Energy is stored in covalent bonds

isooctane or 2,2,4-trimethylpentane



octane number = 100

+

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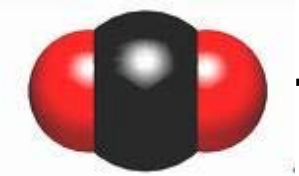

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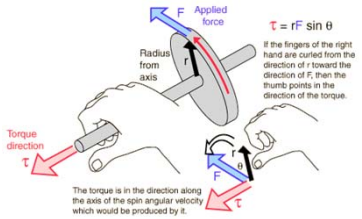

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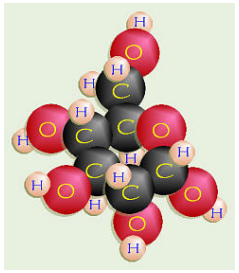

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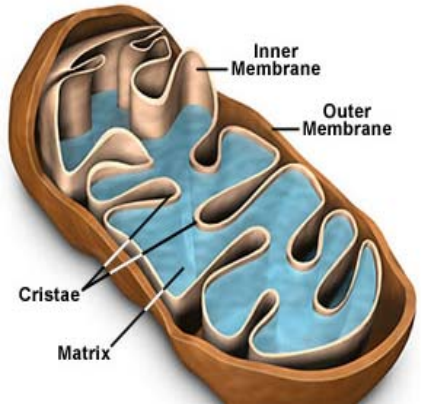
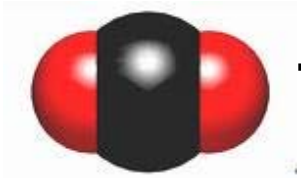


Vitamins and Cofactors
CoQ10
Lipoic Acid
B1, B2, B3, B5, Folate
Fe/S Core, Cu Core

+



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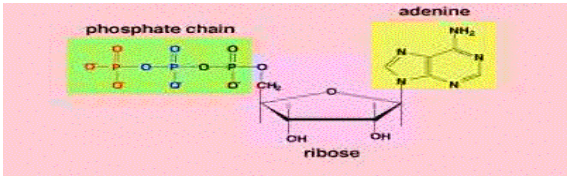

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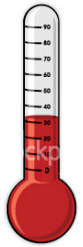

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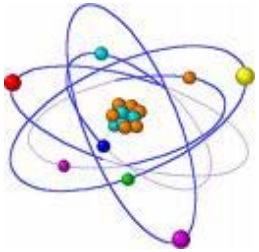
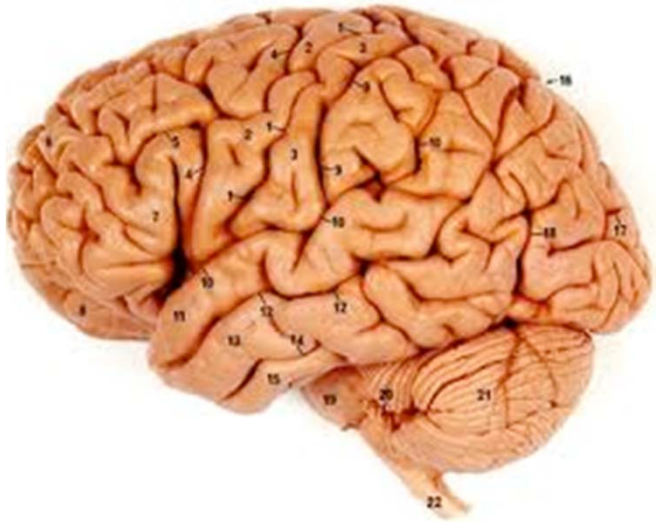
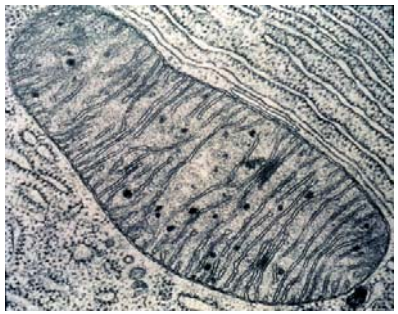
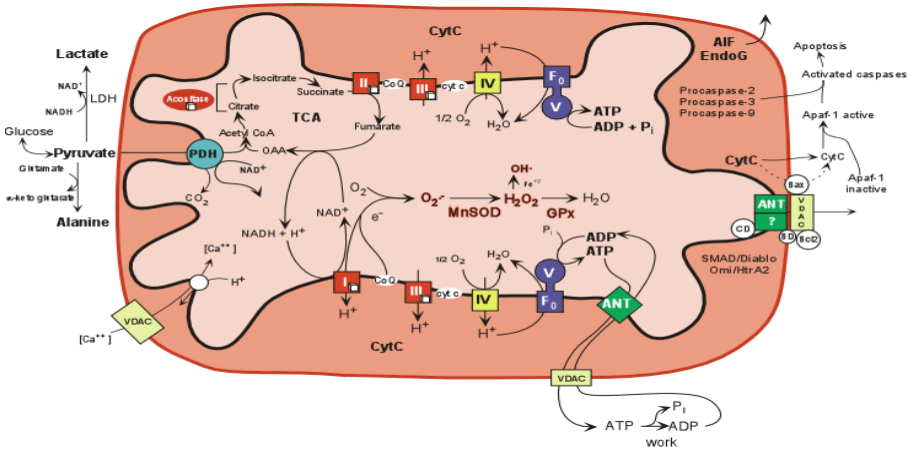


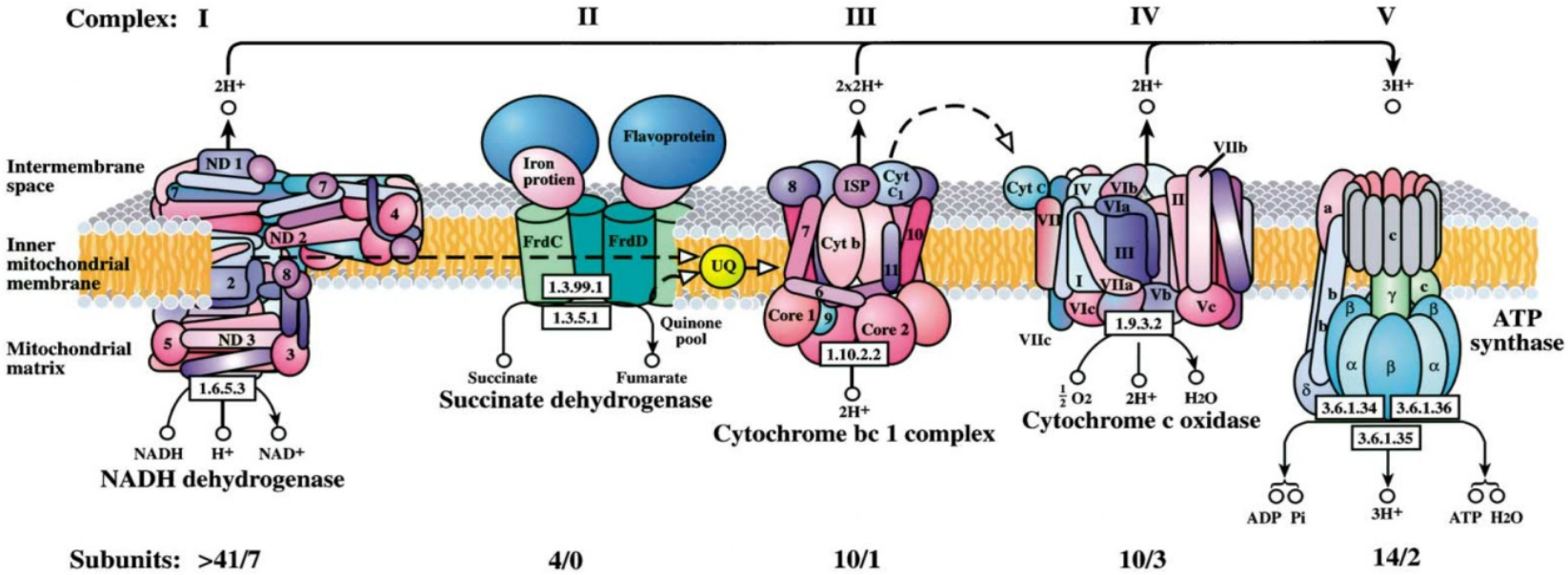


13 Watts
11 kCal/Hr



Carbs, Fats, Proteins + O_2 ⟶ $H_2O + CO_2$ + heat + ATP + intermediates + $O_2^{\bullet}$





The Electron Transport Chain

OXPHOS

ATP Production

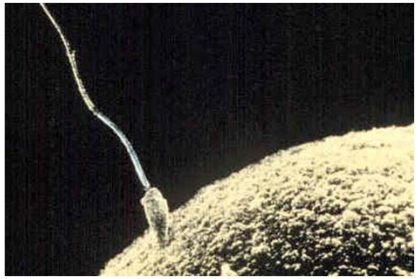
5 Complexes

~100 different proteins

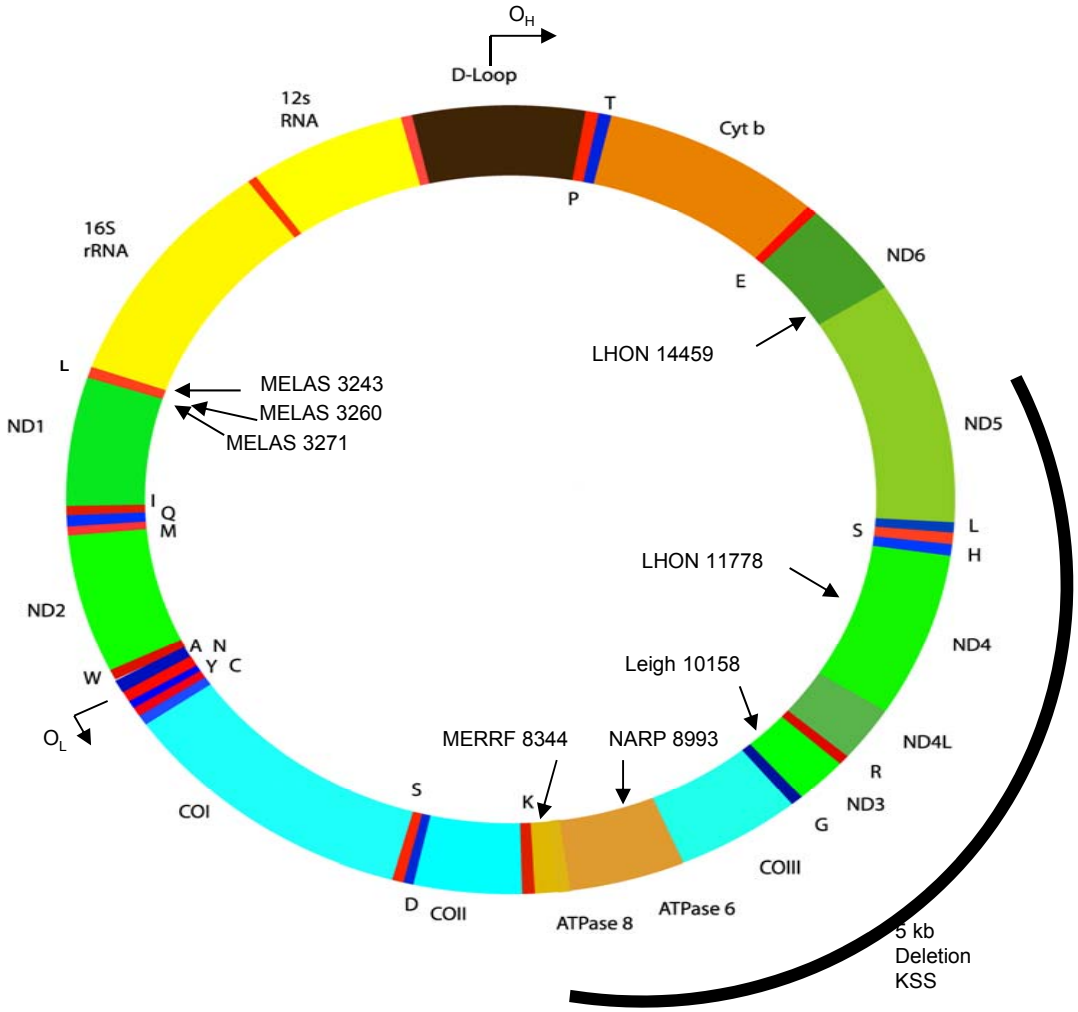
1098 genes supporting the function of the ETC

Mitochondrial Genetics 101

- The mitochondria contain its own DNA
  - Small – 16,569 base pairs
  - 2-10 copies of mtDNA per mitochondria
  - maternally inherited
  - 37 genes
    - 22 tRNAs
    - 2 rRNA
    - 13 proteins
  - some mutations are more harmful than others
  - mutations are not all or none (heteroplasmy)

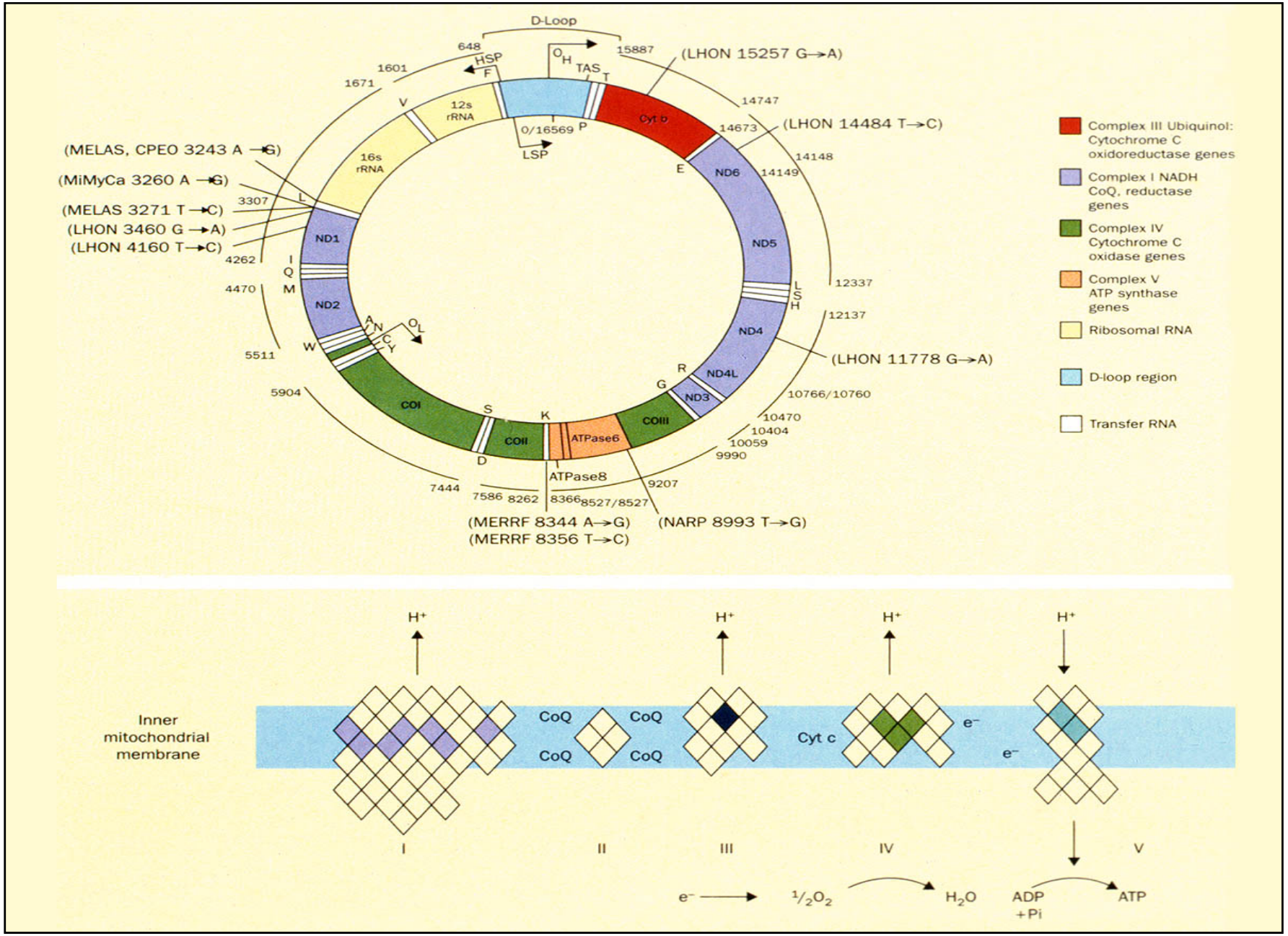


- Only 13 of the ~ 1500 mitochondrial structural proteins are encoded by the mtDNA



Mutation	Clinical Symptons
MELAS 3243 A→G (tRNA-leu)	Stroke-like episodes, type 2 diabetes, deafness, migraines, short stature, encephalopathy (with stress), exercise intolerance, cardiomyopathy.
MELAS 3260 A→G (tRNA-leu)	Similar to MELAS 3243 but cardiomyopathy more common, exercise induced rhabdomyolysis.
MELAS 3271 T→C (tRNA-leu)	Similar to MELAS 3243 (less common).
MERRF 8344 A→G ((tRNA-Lys)	Myoclonus, epilepsy, ataxia, dementia, deafness, neuropathy.
NARP 8993 T→C or T→G NARP/MILS	Adult: Retinitis pigmentosa, ataxia, neuropathy. Child (Leigh's syndrome): Psychomotor regression, ataxia, ophthalmoparesis, ataxic breathing, episodic vomiting and encephalopathy.
Leigh 10158 T→C ND3	Leigh's disease as above for MILS 8993.
LHON 11778 G→A ND4	Painless visual loss over weeks > months, more common in men (onset 20s).
LHON 14459 G→A ND6	LHON as above +/- dystonia.

Complex I subunits
tRNA genes
Complex V subunits
Complex III subunits
Complex IV subunits
rRNA genes


D-Loop
648
HSP
F
1601
1671
V
12s rRNA
16s rRNA
L
3307
4262
I
Q
M
4470
5511
W
A
N
C
Y
O_L
5904
7444
7586
8262
D
S
COI
COII
K
ATPase6
ATPase8
8366
8527/8527
9207
9990
10059
10404
10470
G
R
ND3
ND4L
ND4
10766/10760
12137
H
S
L
12337
E
ND5
ND6
14149
14148
14673
14747
Cyt b
P
0/16569
LSP
O_H
TAS
T
15887
(LHON 15257 G→A)
(LHON 14484 T→C)
(MELAS, CPEO 3243 A →G)
(MiMyCa 3260 A →G)
(MELAS 3271 T →C)
(LHON 3460 G →A)
(LHON 4160 T→C)
(LHON 11778 G→A)
(MERRF 8344 A→G)
(MERRF 8356 T→C)
(NARP 8993 T→G)
Complex III Ubiquinol: Cytochrome C oxidoreductase genes
Complex I NADH CoQ, reductase genes
Complex IV Cytochrome C oxidase genes
Complex V ATP synthase genes
Ribosomal RNA
D-loop region
Transfer RNA
Inner mitochondrial membrane
H+
CoQ
Cyt c
e⁻
I
II
III
IV
V
e⁻ → ½O2 → H2O
ADP +Pi → ATP

The Classic Mitochondrial Phenotype

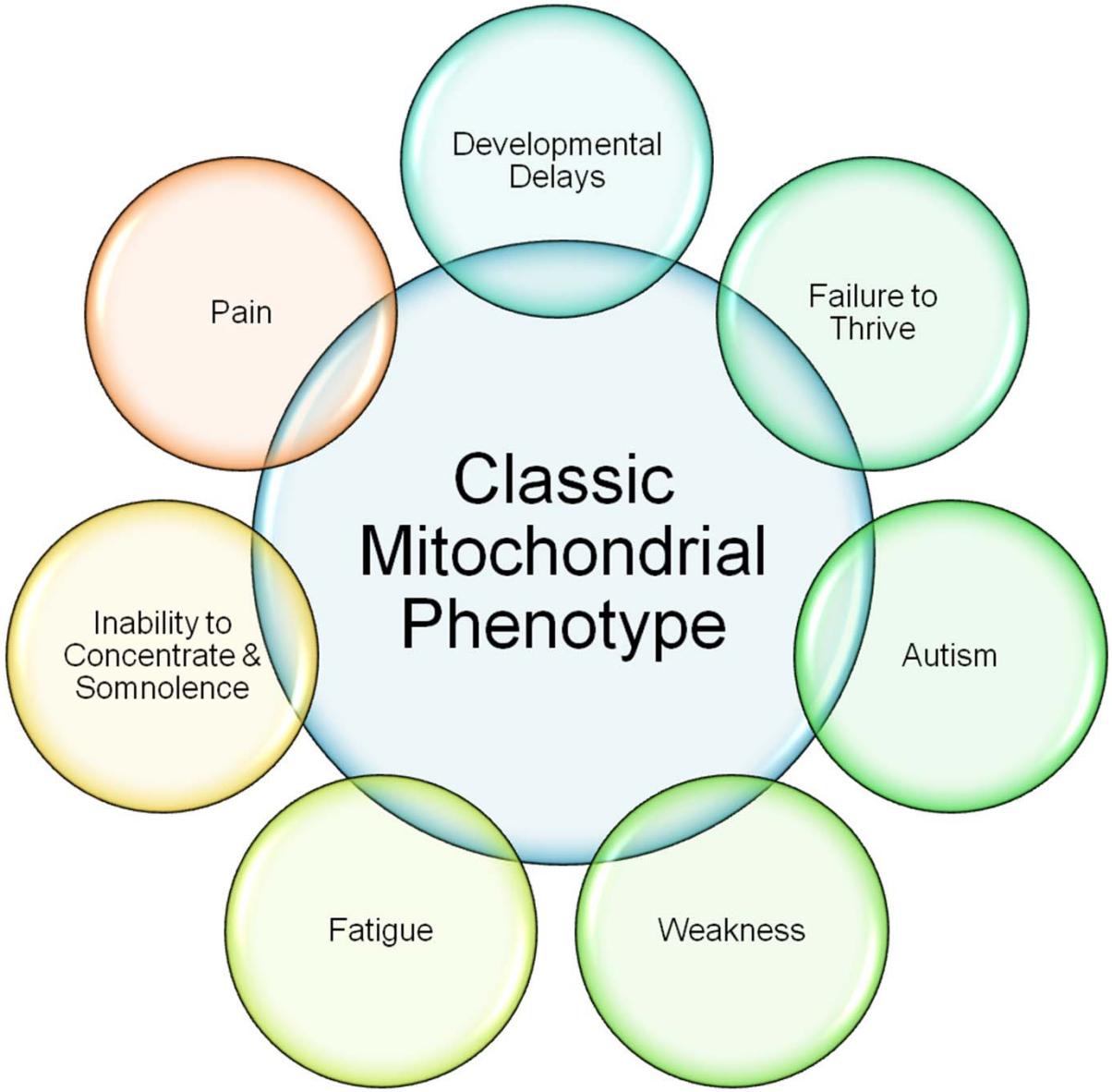

Developmental Delays
Pain
Failure to Thrive
Classic Mitochondrial Phenotype
Inability to Concentrate & Somnolence
Autism
Fatigue
Weakness

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

Other

A newborn, infant, or young child with unexplained hypotonia, weakness, failure to thrive, and a metabolic acidosis (particularly lactic acidosis)
Exercise intolerance that is not in proportion to weakness
Hypersensitivity to general anesthesia
Episodes of acute rhabdomyolysis

TABLE 2 Nonspecific Findings in Mitochondrial Disease

Constitutional
Failure to thrive
Short stature
Intrauterine growth retardation
Microcephaly

Neurologic

Hypotonia
Infantile spasms
Intractable epilepsy
Unexplained movement disorder
Hearing loss (sensorineural)
Axonal neuropathy
Status epilepticus with an additional red-flag or nonspecific feature
Coma
Ototoxicity to certain medications

Cardiovascular

Tachycardia (postural or paroxysmal)

Ophthalmologic

Optic nerve hypoplasia, pigmentary retinopathy

Gastroenterologic

Chronic or cyclic vomiting
Chronic unexplained constipation or diarrhea

Dermatologic

Symmetric lipomatosis

Endocrine

Hypothyroidism
Hypoparathyroidism
Idiopathic growth hormone deficiency

Renal

Renal tubular dysfunction (includes renal tubular acidosis and/or aminoaciduria)
Nephrotic syndrome

Imaging

Unexplained basal ganglia lesions
Unexplained central nervous system atrophy (cerebral or cerebellar)
Unexplained leukodystrophy

Family history

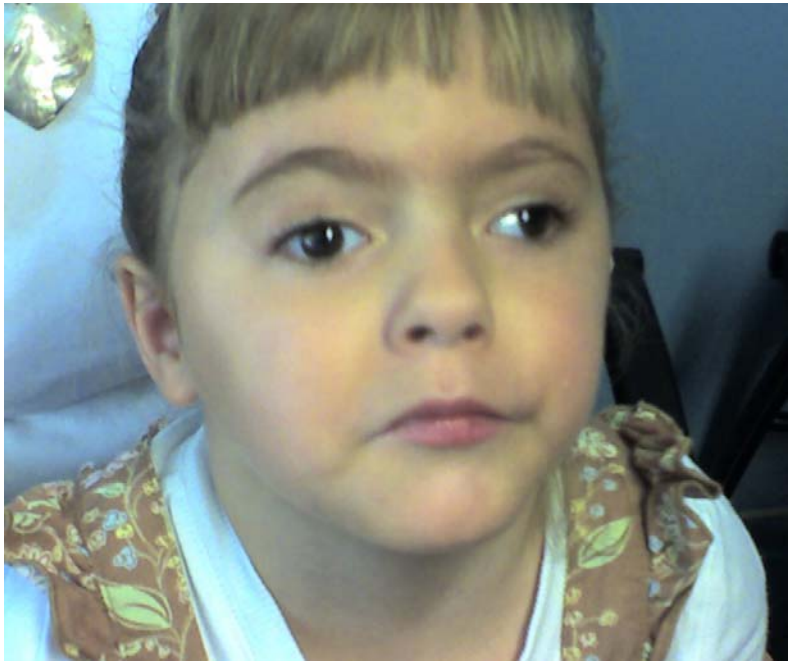
Sudden infant death syndrome
Multigenerational maternal inheritance pattern

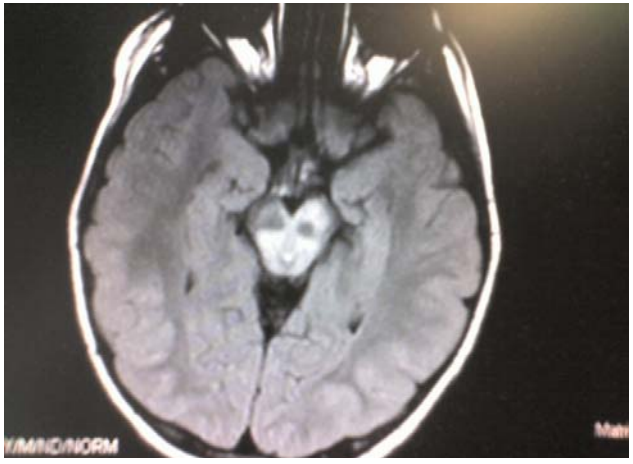
Richard H. Haas, Sumit Parikh, Marni J. Falk, Russell P. Saneto, Nicole I. Wolf, Niklas Darin, Bruce H. Cohen
PEDIATRICS Volume 120, Number 6, December 2007


Classic Mitochondrial Disorders

Leigh Syndrome

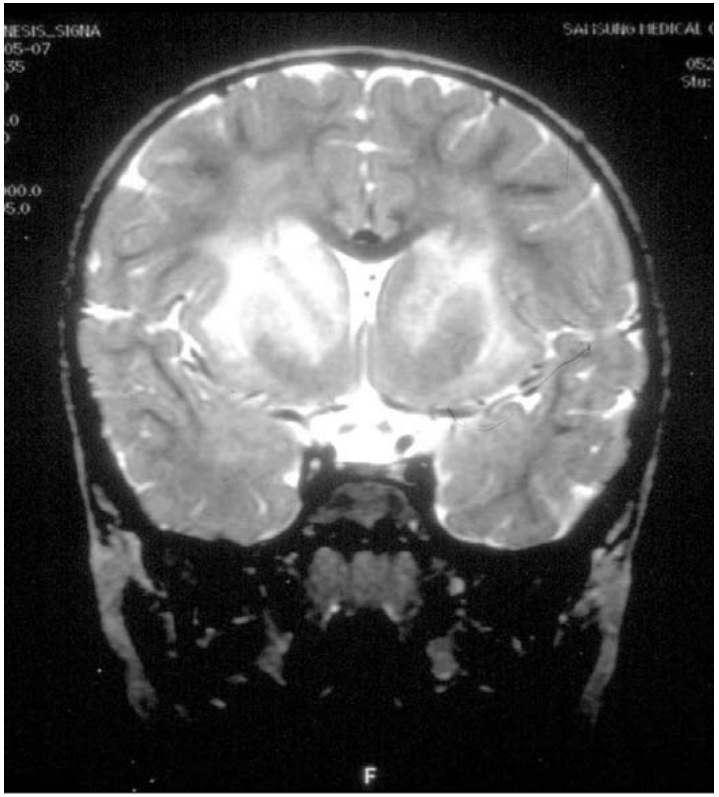
- Healthy child until age 3
- Non-specific viral infection
- Lost the ability to ambulate due to ataxia, hemiparesis then bilateral hemiparesis
- lactic acidosis
- eye movement and bulbar dysfunction
- dystonia
- neuropathy
- some recovery over 6 months followed by deterioration
- muscle biopsy may be normal unless due to complex IV defects
- clinical: heavily CNS/PNS during the natural life span
- host of mtDNA, nDNA mutations result in this presentation
- not clear why some mutations cause Leigh Syndrome and others do not



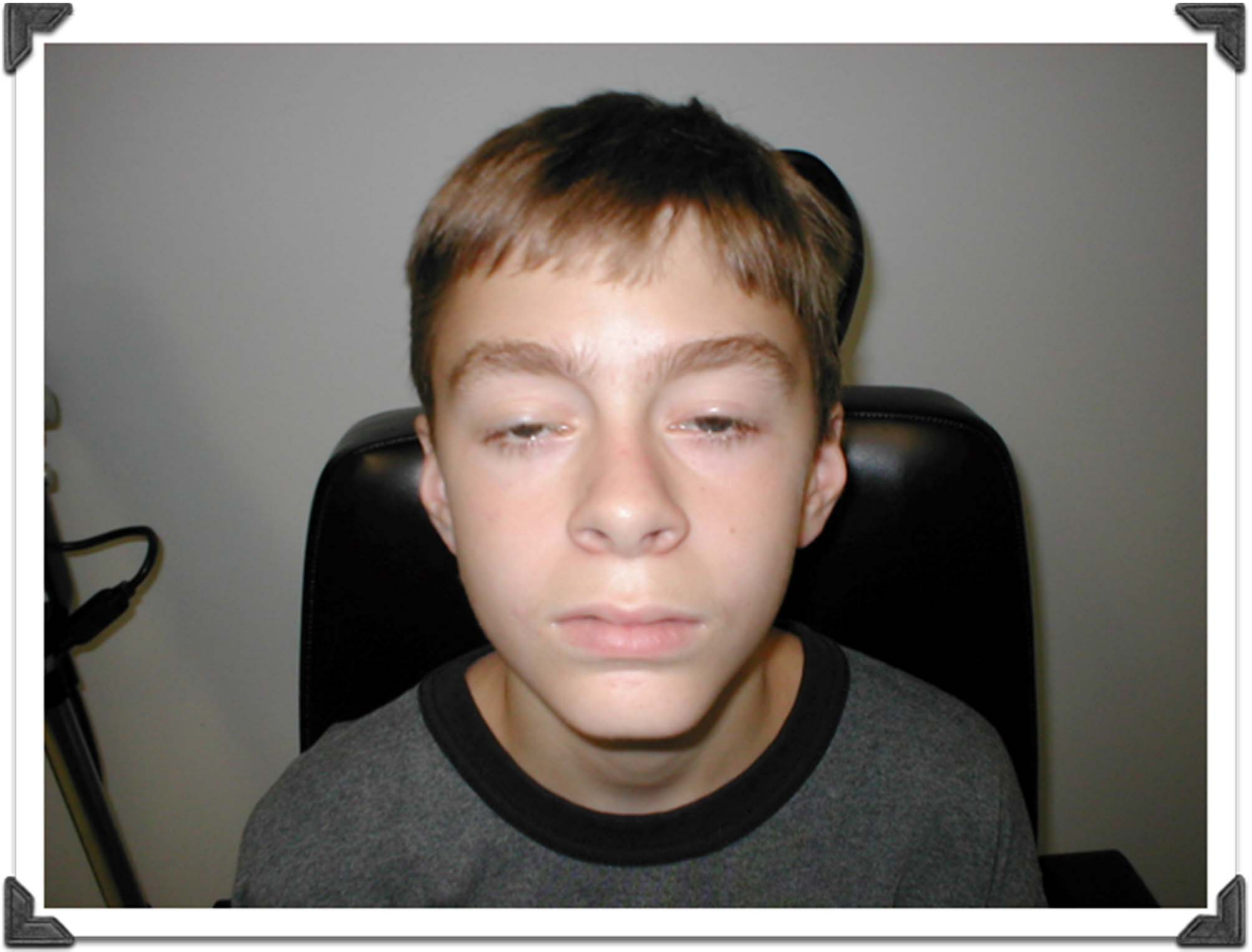


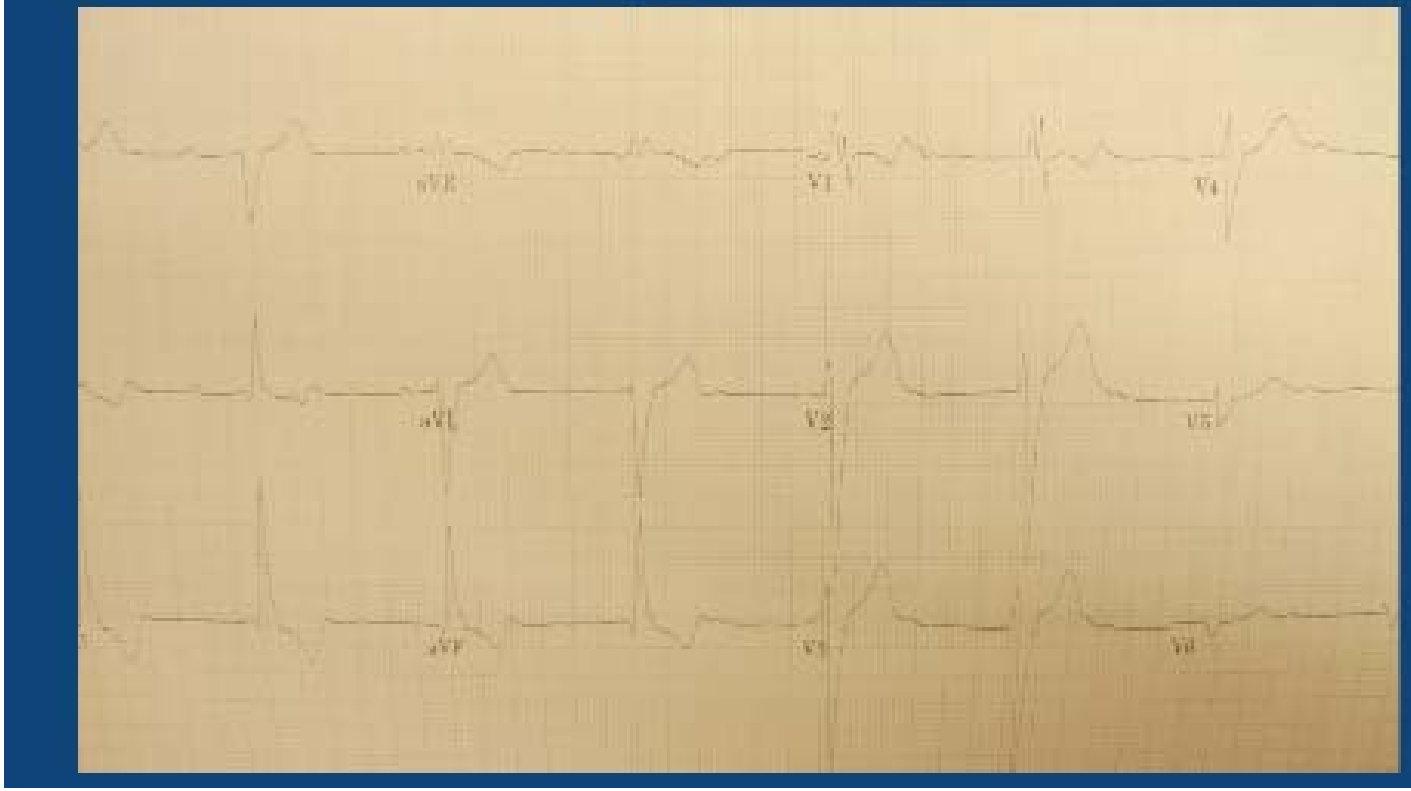
Leigh, D. :
Subacute necrotizing encephalomyelopathy in an infant. J. Neurol. Neurosurg. Psychiat. 14: 216-221, 1951

Leigh Syndrome

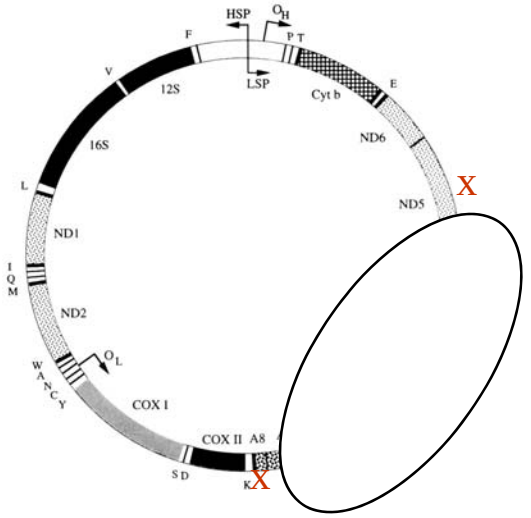


4 yo boy with ataxia after
viral infection showing
deep gray matter involvement




aVR
V1
V4
aVL
V2
V5
aVF
V3
V6

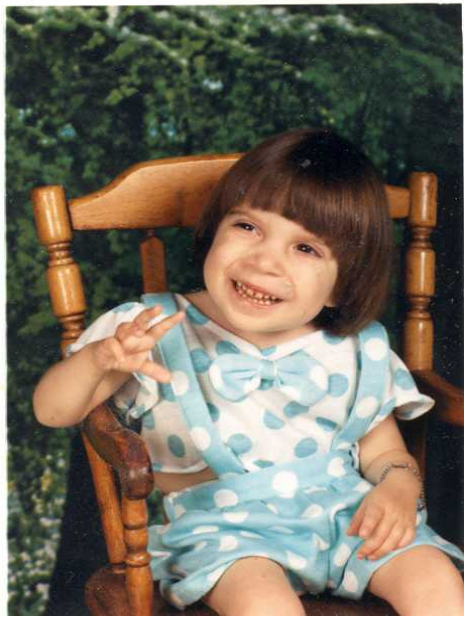
Kearn Sayre Syndrome



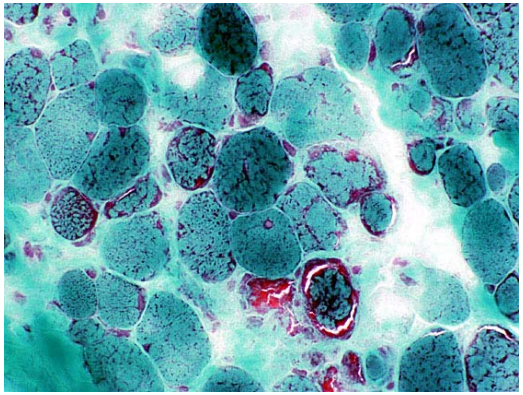
- Triad
  - high frequency hearing loss
  - Retinitis pigmentosa
  - PEO
- Other features
  - myopathy
  - diabetes
  - retinopathy
  - dementia and seizures
  - cardiomyopathy
  - dysphagia and weight loss
- 5 kB deletion in all (>97%) of the mtDNA from middle of ND5 to ATP8; (4977 base pairs from 8488 to 13460; 13 base pair repeat at mutation break point)

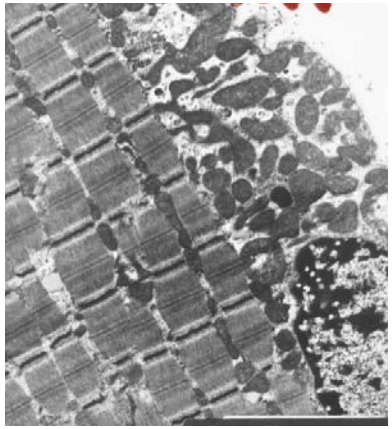
Kearns T, Sayre G (1958). "Retinitis pigmentosa, external ophthalmophegia, and complete heart block: unusual syndrome with histologic study in one of two cases". A.M.A. Archives of Ophthalmology 60 (2): 280-9

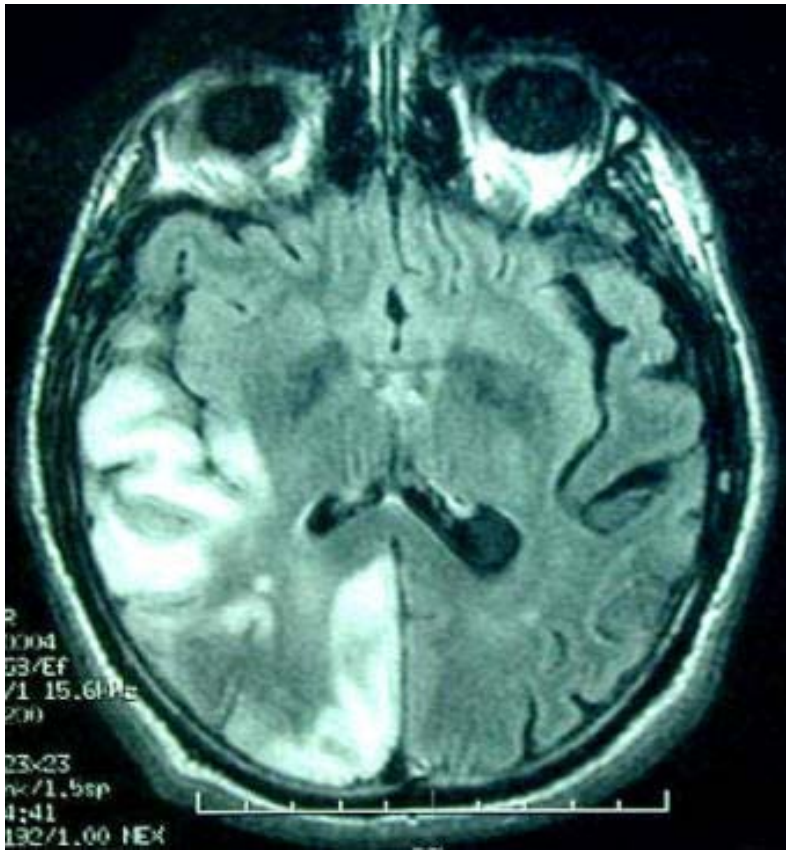
Pearson Syndrome



- My index patient
- DOB 6/20/82
- Anemia (Hb 8) and FFT noted at 8 months
- Presented with severe lactic acidosis (8 mmol/l)
- Sideroblastic anemia
- digestive problems
- moderate mental retardation
- myopathy
- neuropathy
- ptosis and later PEO
- progressive hearing loss
- diabetes mellitus
- heart block
- cardiomyopathy
- died in 1995
- definitive diagnosis showing common KSS deletion 1993





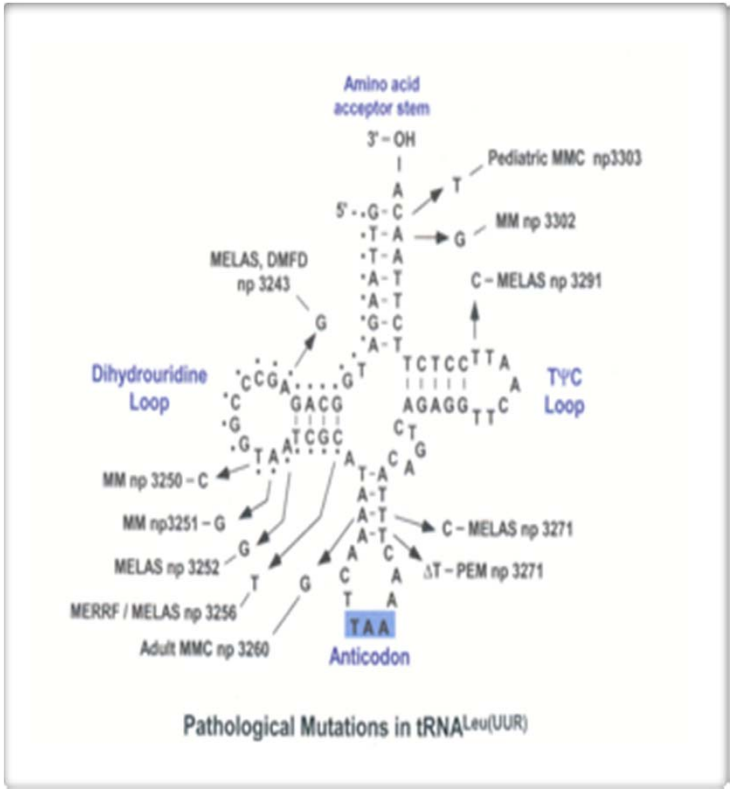


MELAS

MELAS - a mtDNA point mutation disorder

Family History Gives Clues

- 5 yo girl; birth weight 6'15"
- Mother; 33 with DM2, bipolar disease, fibromyalgia, hearing loss
- sat @ 7 mo, walked @ 16 mo, 1st words at 15 mo, sentences at 22 months
- FTT
  - required ng-tube at age 31 months ➟g-tube
- Age 3 -EKG: WPW
  - Cardiac ablation performed
- Status epilepticus at age 4
  - MRI showed a focal abnormality in the left occipital lobe
- Lactic acid elevated

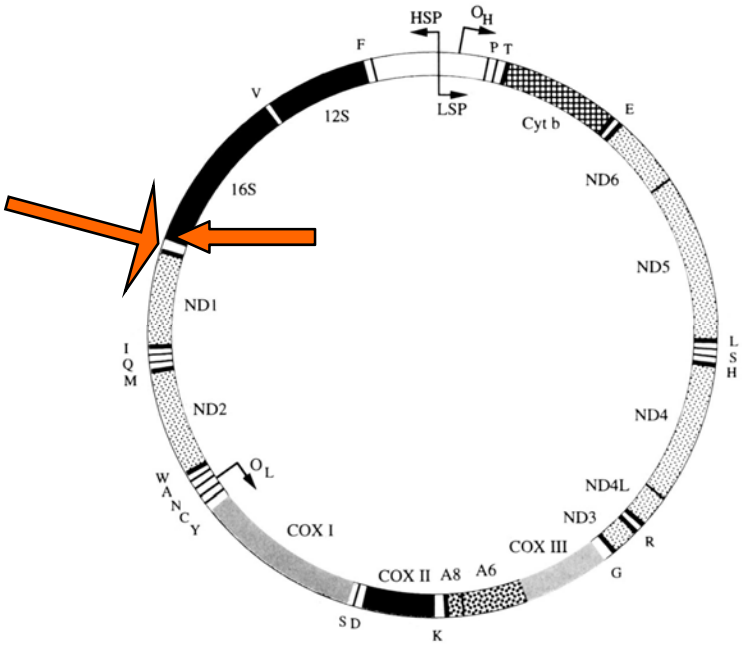


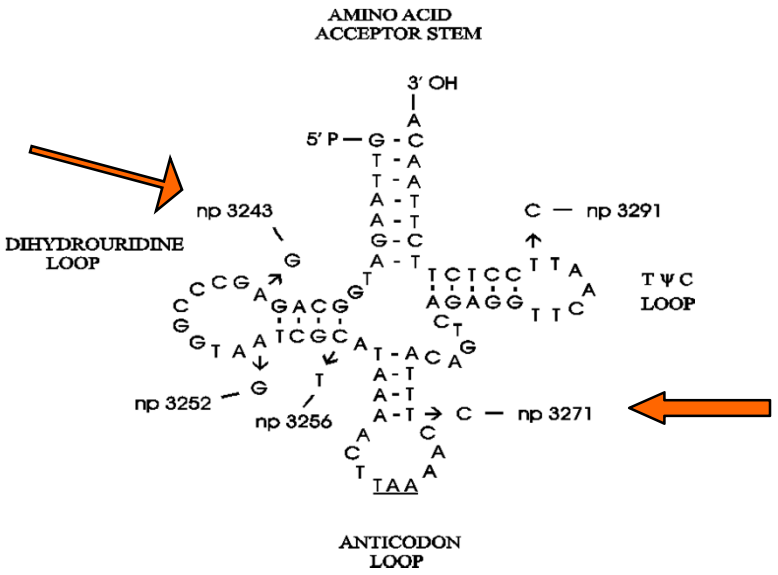
Pathological Mutations in tRNA$^{Leu(UUR)}$

MELAS

- Variable Age of Onset (4 months through adult)
  - FTT and DD in infancy, ADD common
  - weakness and fatigability
  - Short Stature
  - Strokes and stroke-like episodes
  - Progressive Dementia
  - Hearing loss and DM
  - Anorexia from autonomic gut neuropathy
  - Migraine
  - Myoclonic or tonic-clonic seizures
  - WPW, hypertrophic > dilated cardiomyopathy
  - Ophthalmoplegia
  - RTA

- A3243G tRNALeu (UUR) gene; 1: 6135 (Finnish) (80%) to up 1:5000
- C3271G tRNALeu (UUR) gene
- > 20 other mtDNA mutations causing this disorder





Pavlakis SG, Phillips PC, DiMauro S, et al: Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes: a distinctive clinical syndrome. Ann Neurol 1984 Oct; 16(4): 481-8

Why Should You Listen Now?

Because 2% of people carry 1 mutation in this gene

Case Report

- 15 year old young woman evaluated for jerky limb movements -- diagnosis was “mannerisms” (1993)
- At age 19, patient has her first seizure (1997)
  - EEG multifocal spikes
  - MRI normal
  - started on carbamazepine - ineffective
  - changed to valproate
- Three months later
  - florid liver failure
  - undergoes a liver transplant

Case Report

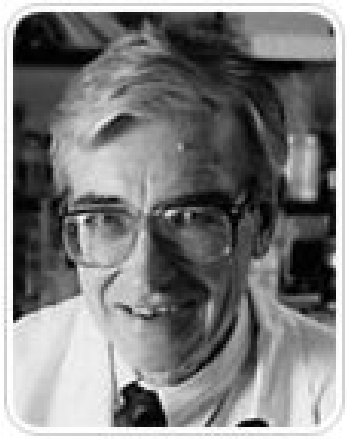
- Muscle biopsy and mitochondrial evaluation @ Emory
    - biochemical defects identified
    - genetic evaluation normal started on supplements
- 1998: My first office visit
    - seizures, poorly controlled
    - jerky movements, appeared both like myoclonus or chorea
    - bright, energetic
    - returned to college, working in the radio business
- 2000: No Change
- 2002: No Change

Case Report

- November 2005
    - symptoms and signs
        - seizures better controlled
        - PEO - scheduled for surgery
        - slurred speech
        - ataxia
        - poor night vision
        - hearing loss
        - memory difficulties
        - inability to maintain employment
        - loss of DTRs

Step back 75 years

Alpers Syndrome



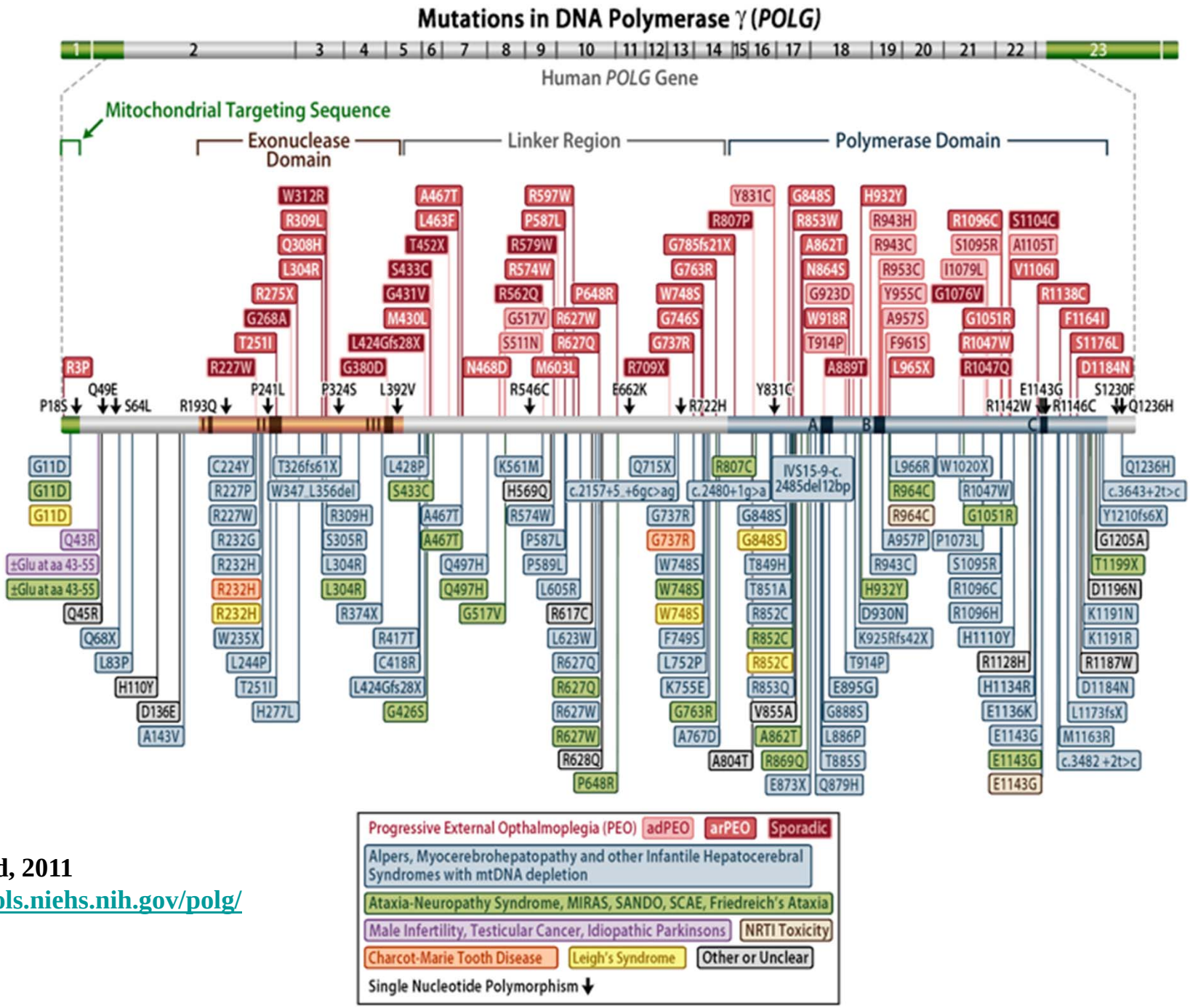
- Infantile fatal cerebral disorder that was first described by Bernard Alpers in 1931; “poliodystrophy” -- refractory seizures, developmental regression, cortical blindness, age of onset 3-7 years, some with identified developmental disabilities and others normal
- 1975 - study showing mitochondrial ultrastructural changes in Alpers poliodystrophy
- 1976 Huttenlocher described the hepatic features (micronodular necrosis) and familial nature of the disorder; “Huttenlocher variant” or “Alpers-Huttenlocher syndrome”
  - Based on pattern of illness - autosomal recessive
  - many children present with epilepsia partialis continua or status epilepticus
  - progressive neuropathy and spasticity
  - Death 1-20 years into the course, often from liver failure

B. J. Alpers. Diffuse progressive degeneration of the grey matter of the cerebrum. Archives of Neurology and Psychiatry, Chicago, 1931, 25: 469-505.

Alpers Poliodystrophy

- 1992 Bicknese et al describe fatal valproate toxicity in a boy with “Huttenlocher variant of Alpers' syndrome”
- 1996 Copeland characterizes and clones human the polymerase gamma gene
- 1996 Naviaux reported in abstract form biochemical evidence of mitochondrial dysfunction
- 2001 First mutations described in this gene causing progressive ophthalmoplegia
- 2004 Naviaux et al find several families with Alpers harboring 7 distinct mutations in polymerase gamma (*POLG)* Naviaux, Nguyan POLG mutations associated with Alpers' syndrome and mitochondrial DNA depletion. Ann Neurol 55: 706-712; 2004.

and one year later…..



Copeland, 2011

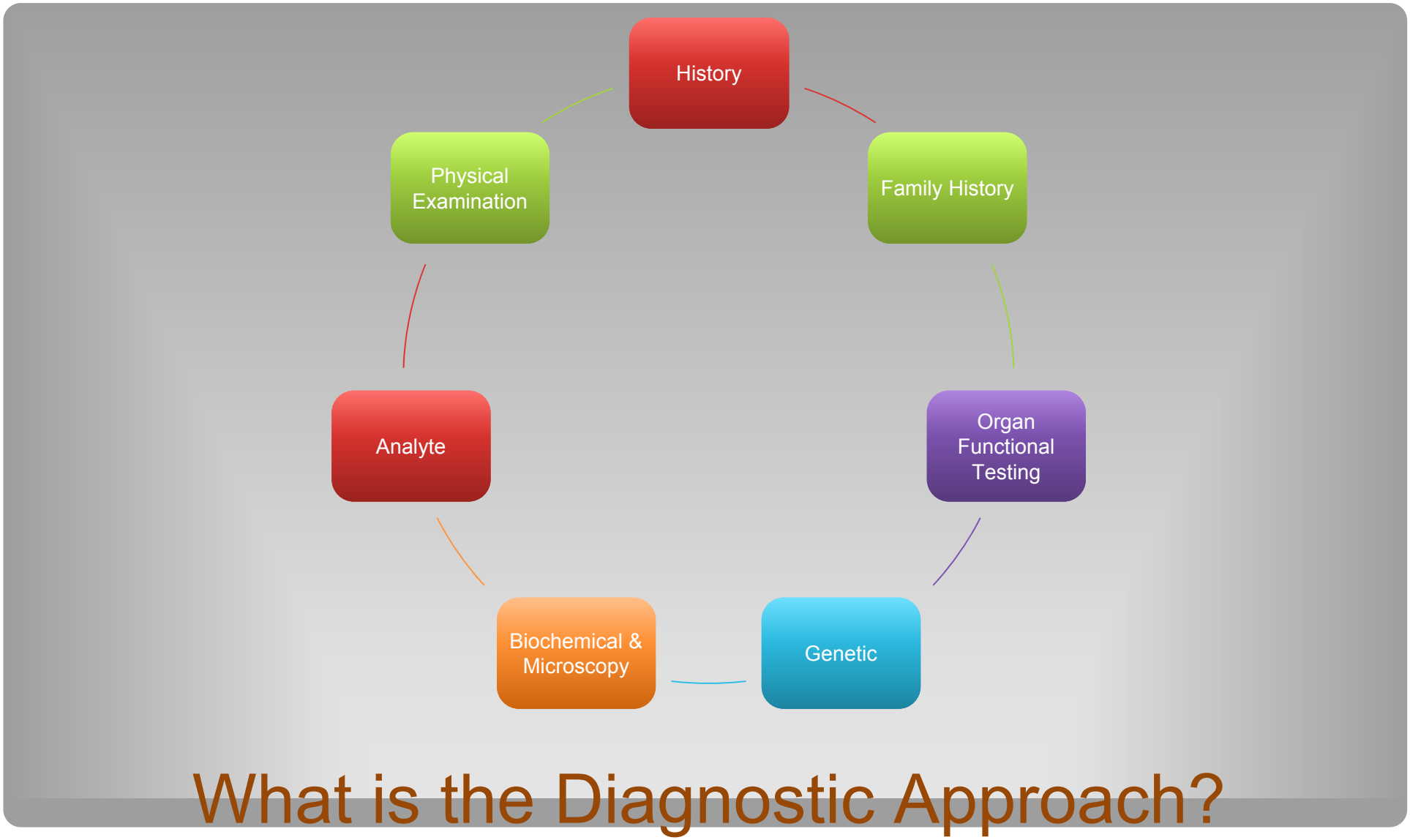
http://tools.niehs.nih.gov/polg/

Table 2. Clinical features in patients with *POLG* mutations

System	Feature
Psychiatric	Depression
	Psychosis
	Dementia
Seizures	Myoclonus
	Focal motor seizures
	Generalized seizures
	Status epilepticus
Extrapyramidal	Parkinsonism
	Chorea
Cerebellum	Ataxia
'Cerebrovascular'	Migraine
	Stroke-like episodes
Special sensory	Sensorineural deafness
	Retinopathy
	Cataract
Muscle	Ptosis and external ophthalmoplegia
	Proximal myopathy
	Exercise intolerance
Peripheral nerve	Sensory neuronopathy/ganglionopathy
	Axonal sensorimotor neuropathy
Endocrine	Diabetes
	Primary ovarian failure
	Primary testicular failure
Gastrointestinal	Liver failure
	Gastrointestinal dysmotility
Cardiac	Cardiomyopathy

Hudson and Chinnery Hum Mol Genet 2006;15:R244-252

October 2006



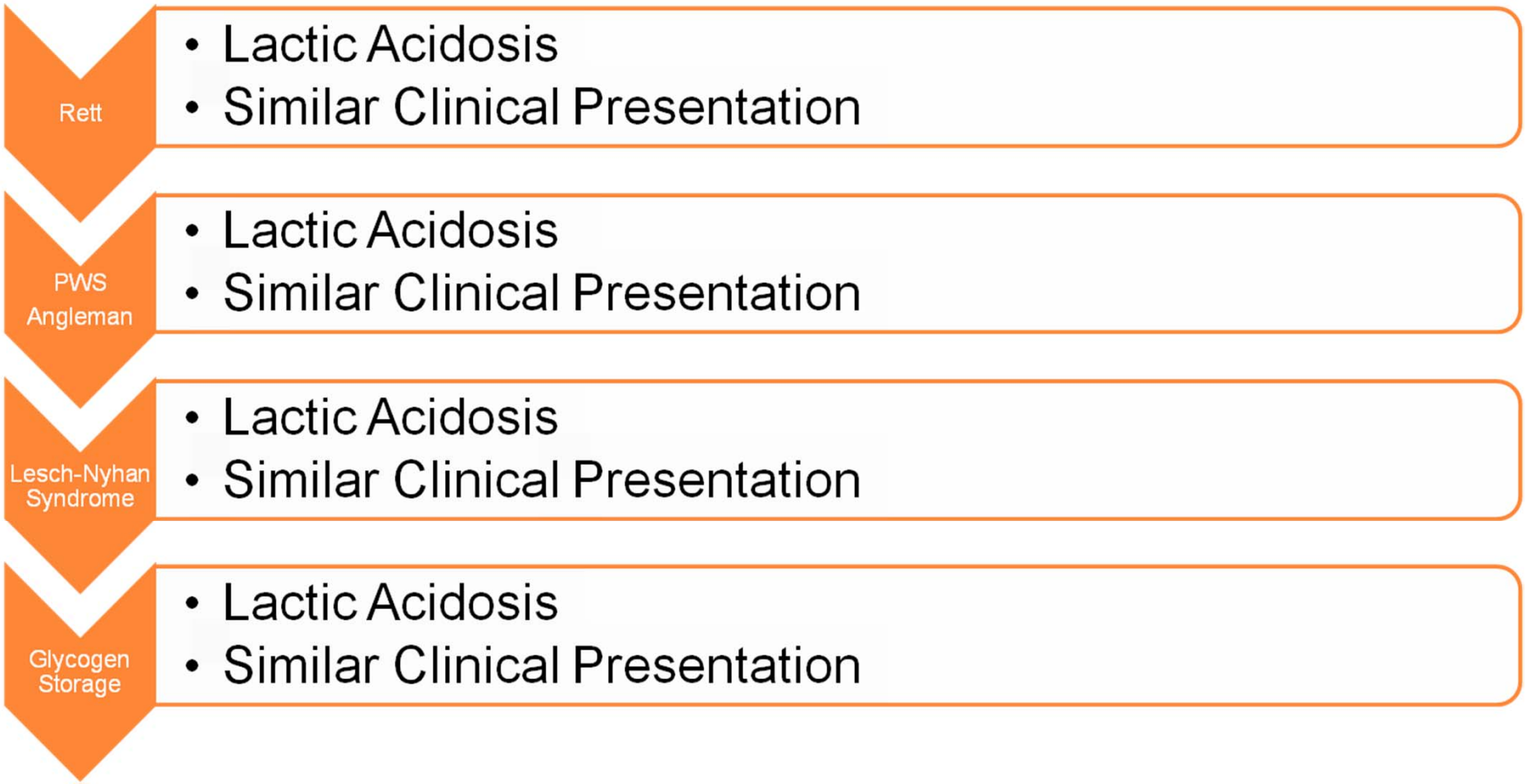
What is the Diagnostic Approach?

Diagnosis: Biomarkers

- Lactic acid (plasma, CSF, urine) increased
- Lactate:Pyruvate ratio increased
- Abnormal amino acid pattern (□alanine, alanine:lysine, proline, sarcosine, glutamine and □arginine, citrulline_
- Abnormal organic acids
- Low carnitine, abnormal acylcarnitine patterns

Abnormal results are not specific
Normal results are not sensitive to eliminate the diagnosis

When Should We Think of Something Else?



A Typical Lab Evaluation: 1989-

Blood
Lactic Acid
Amino Acids
Total and Free carnitine with acylcarnitine profile
B12 level
Methylmalonic acid
Ammonia
CK
CMP + ? HBA1C
CBC
CoQ10 (WBC)
Free T4 + TSH

Urine
Routine Urine Analysis
Organic Acids
Amino Acids
Carnitines + Acylcarnitine Profile
Acylglycine
Guanidoacetate + Creatine
Purine and Pyrmidines

Skin biopsy for EM & Fibroblast Culture: acylcarnitne probe

Dysmorphic + Cognitive Problems? → **aCGH** → OR → **Fragile X**, **SCN1A**, **Rett**, **Prader-Willi / Angelman**, **CSF Neurotranmitter Disorder**, **Disorders of Glycosolation**

Muscle Biopsy

Specific mtDNA Disorder? → **Specific mtDNA point mutation or LR-PCR**

Maternal Pattern? mtDNA-spectrum? → **Whole Mito Genome**

Specific nDNA Disorder? → **Specific nDNA gene sequence**

NextGen Expanded Nuclear Gene Testing

A Typical Lab Evaluation: 2013

Blood
Lactic Acid
Amino Acids
Total and Free carnitine
B12 level
Methylmalonic acid
Ammonia
CK
CMP + ? HBA1C
CBC
CoQ10 (WBC)
Free T4 + TSH

Urine
Routine Urine Analysis
Organic Acids
Guanidoacetate + Creatine

Dysmorphic
+
Cognitive Problems?

aCGH

OR

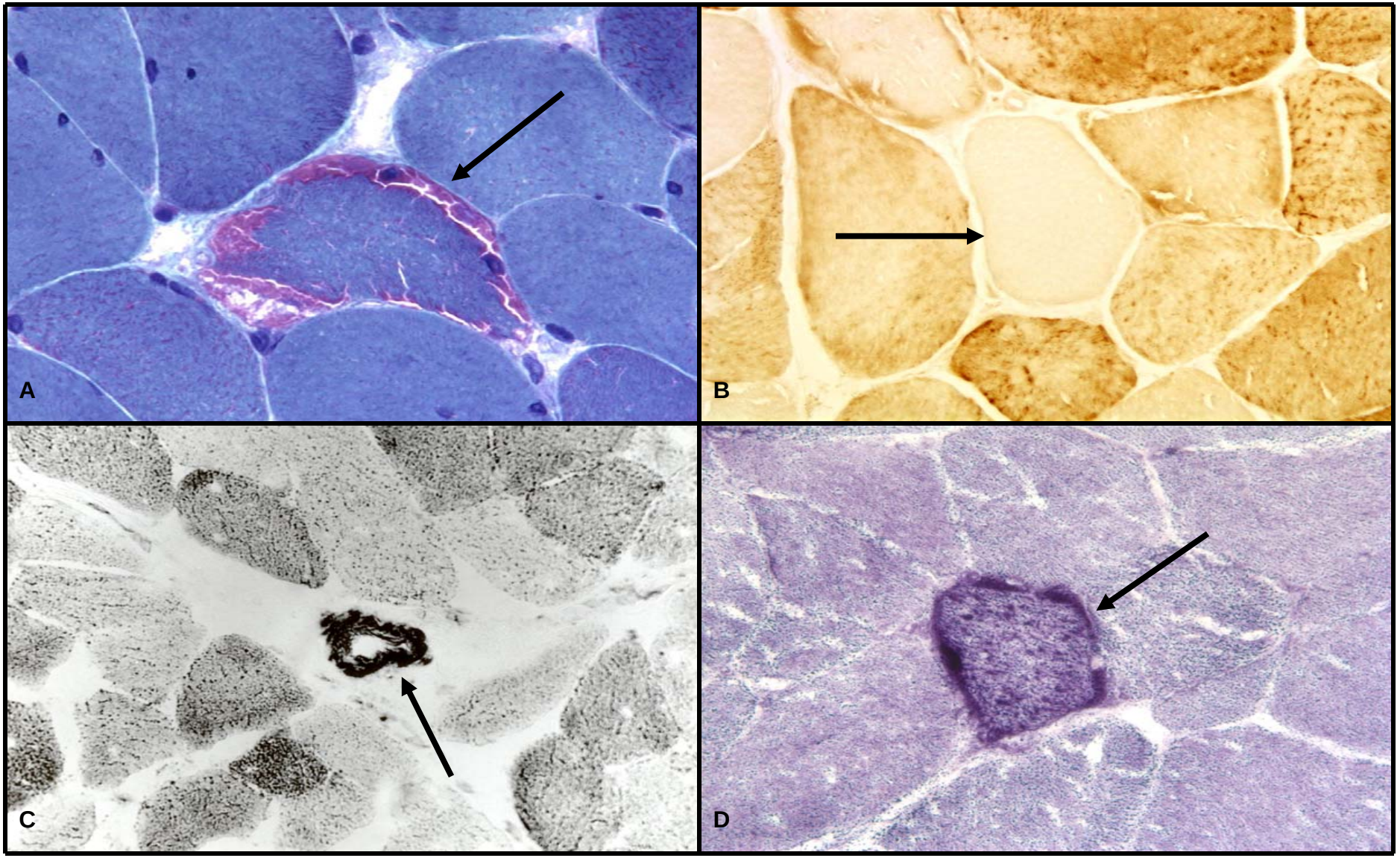
Fragile X
SCN1A
Rett
Prader-Willi / Angelman
CSF Neurotranmitter Disorder
Disorders of Glycosolation

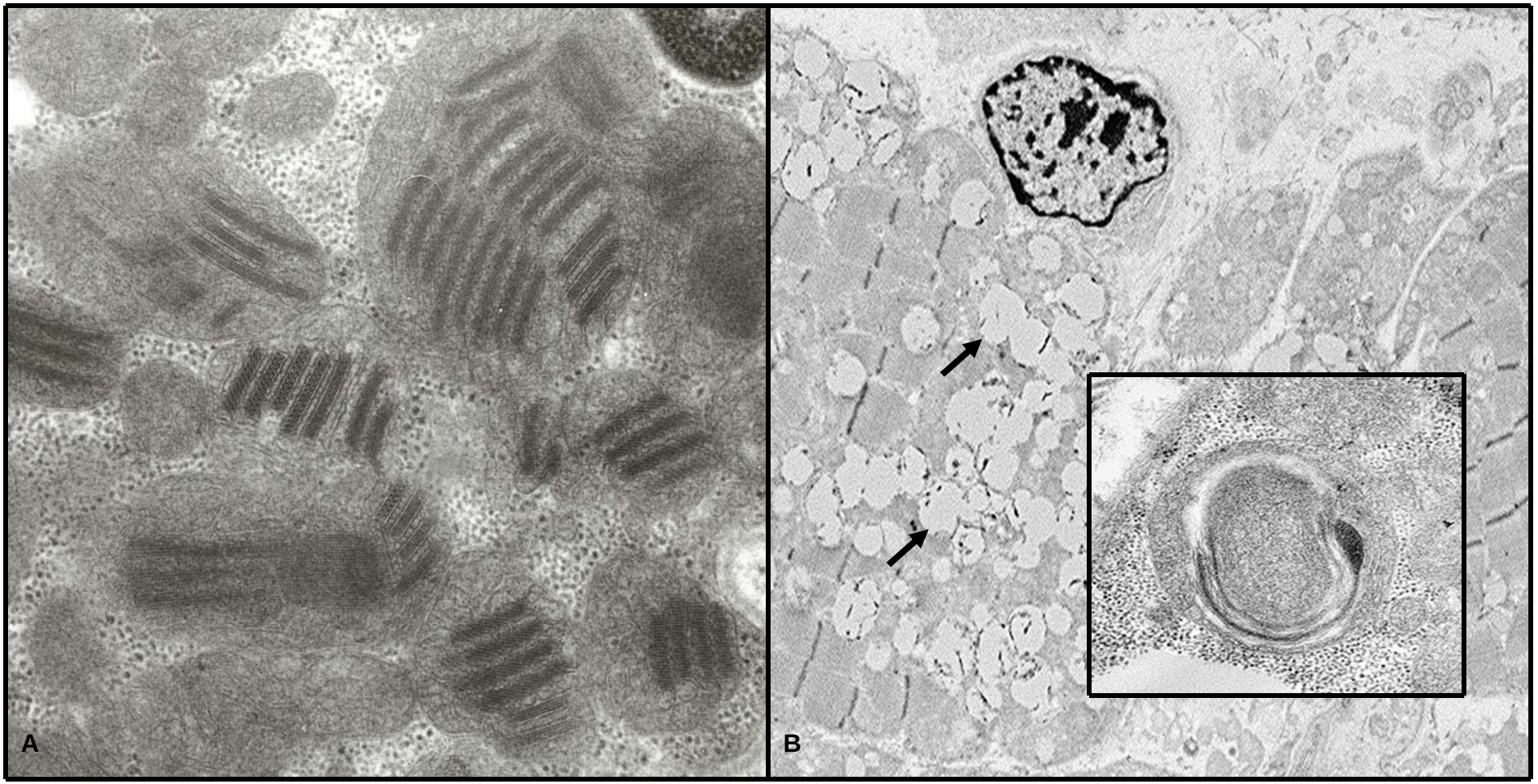
Maternal Pattern?
mtDNA-spectrum?

Whole Mito Genome

NextGen Expanded Nuclear Gene Testing

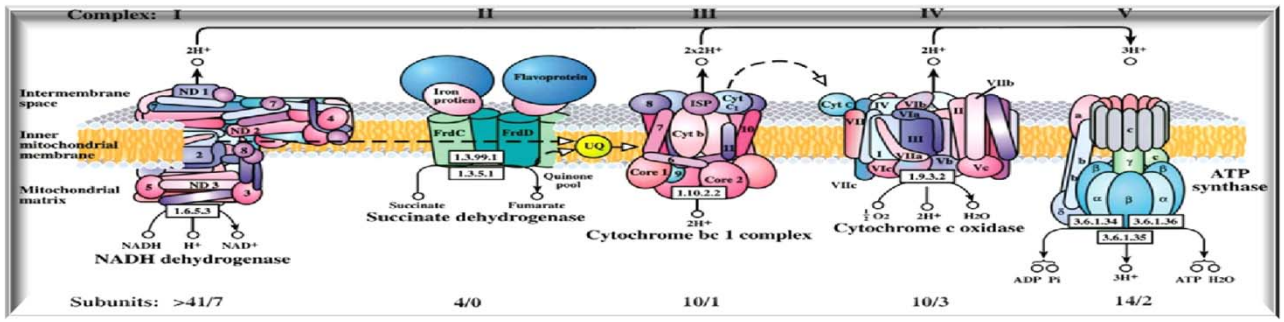
THE POWER OF THE MUSCLE BIOPSY


A
B
C
D

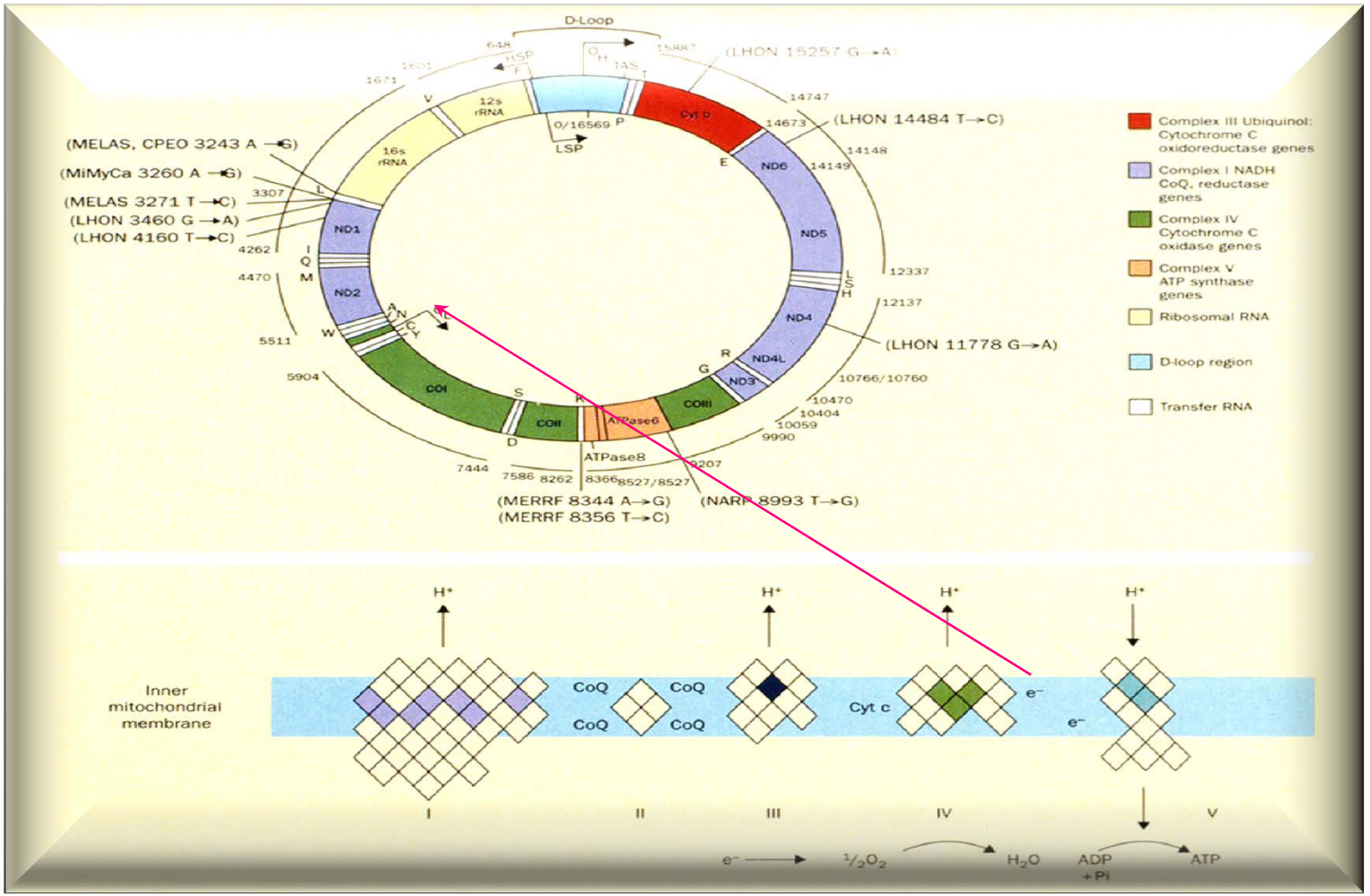

A
B

DB

	ETC Complexes	Patient	Control	Activity (µmol/min/g wet weight) Prior Controls Mean ± SD N= 12	Range		
NADH-cytochr. c reductase - rotenone:		562.0		805.0 ± 112.8	(639.0 - 915.0)		L
NADH-cytochr. c reductase + rotenone:		555.9		324.0 ± 119.0	(188.0 - 441.0)	H	
NADH-cytochr. c reductase rot. sens.:	I, III	6.1		481.0 ± 36.5	(441.0 - 528.0)		L
NADH-ferricyanide reductase	I	2180.5		1620.5 ± 363.8	(1284.0 - 2131.0)	H	
Succinate-cytochrome c reductase:	II, III	59.2		146.4 ± 41.6	(82.0 - 187.0)		L
Succinate dehydrogenase:	II	177.2		74.5 ± 30.4	(53.0 - 96.0)	H	
Decylubiquinol-cytochrome c reductase:	III	5049.0		4327.5 ± 415.1	(4034.0 - 4621.0)	H	
Cytochrome c oxidase:	IV	38083.0		73307.4 ± 22667.2	(38411.0 - 96774.0)		L
Citrate Synthase:		2408.8		1820.3 ± 348.2	(1338.0 - 2555.0)		



Thanks to Charles Hoppel, MD; CIDEM


D-Loop
HSP
LSP
12s rRNA
16s rRNA
Cyt b
ND6
ND5
ND4
ND4L
ND3
COIII
ATPase6
ATPase8
COII
COI
ND2
ND1
(LHON 15257 G→A)
(LHON 14484 T→C)
(LHON 11778 G→A)
(MELAS, CPEO 3243 A→G)
(MiMyCa 3260 A→G)
(MELAS 3271 T→C)
(LHON 3460 G→A)
(LHON 4160 T→C)
(MERRF 8344 A→G)
(MERRF 8356 T→C)
Complex III Ubiquinol: Cytochrome C oxidoreductase genes
Complex I NADH CoQ, reductase genes
Complex IV Cytochrome C oxidase genes
Complex V ATP synthase genes
Ribosomal RNA
D-loop region
Transfer RNA
Inner mitochondrial membrane
CoQ
Cyt c
e⁻
H⁺
I
II
III
IV
V
ADP +Pi
ATP
H₂O

Muscle Biopsy Concepts

- If you are going to do a muscle biopsy, do it right
- Myopathic Disorders often warrant a biopsy
- Although there is a role for genetic testing, whole exome is not going to replace the value of a muscle biopsy any time soon
- Common Errors
  - Not correlating pathological findings with biochemistry
  - Over-interpreting citrate synthase levels
  - Deriving answers with mathematical manipulation of data
  - Performing biochemical testing on tissue that has thawed or was not frozen properly

Primary vs. Secondary Mitochondrial Disease

- Definition now a subject of hot debate for both scientific and political reasons
- Primary
  - those disorders directly affecting the electron transport chain and those disorders caused by pathogenic mutations in the mtDNA or respiratory chain encoded nDNA
    - Electron Transport Chain enzymology without confirmatory histologic data will not be accepted in most circumstances
- Secondary
  - those disorders that affect mitochondrial function by other mechanisms
    - indirect
    - mutations outside the exome
    - SNPs (disease modifying mutations)
  - complex I defects without other evidence, single mutations in most genes, drug toxicity

- Developmental Regression with lactic acidosis≥a≤ or elevated CSF lactate
- KSS phenotype (muscle better tissue than blood)
- LHON, NARP, MELAS, MERRF or Leigh phenotype
  - where screening for the common mutations is not informative
  - as an initial test
- Epilepsia Partialis Continua -Status Epilepticus-Refractory Seizures when POLG is normal
- Caudal-Cephalic MRI progression
- maternal inheritance pattern or similarly affected siblings
- Developmental Regression in the setting of prior normal development and non-dysmorphism
- > 3 objective signs in > 2 organ systems

≥a≤ **elevated alanine, alanine:lysine > 4, abnormal organic acids (CAC, 3-MG, lactate, pyruvate); note that lactate is often elevated in mutations involving tRNA but not the mtDNA mutations that encode for respiratory chain proteins**

When to do mtDNA sequencing?

When to Consider *POLG*?

Child

- Developmental Regression
- Epilepsia Partialis Continua -Status Epilepticus-Refractory Seizures
- Cephalic-Caudal MRI progression
- Valproate-induced liver toxicity
- Cortical Blindness
- Myoclonus
- Ataxia
- Neuropathy
- Liver Failure

Adult

- PEO
- myopathy
- psychiatric illness
- Parkinsonism or EP movement
- ataxia
- dysarthria
- seizures
- DM
- ataxia - dysarthria
- neuropathy
- myoclonus
- dementia

- Strong story for mitochondrial disease with negative prior testing
- Strong story for neurogenetic disorder with a large differential
- Evidence on a muscle ETC enzyme test of an abnormality, but with normal mtDNA
  - Complex I nuclear genes and assembly genes
  - Complex IV nuclear genes and assembly genes

When to Consider NextGen Mitochondrial Testing?

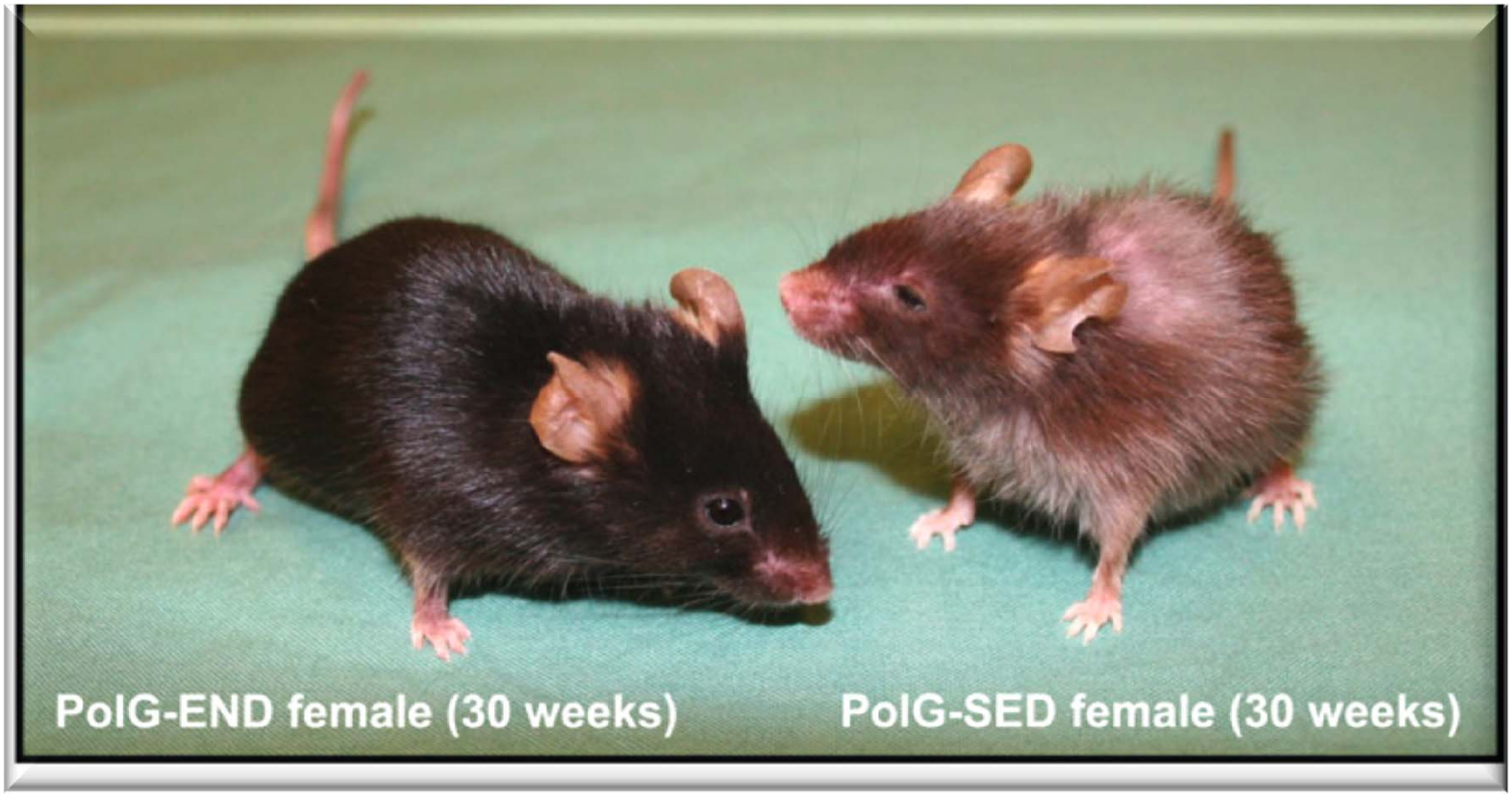
...but it comes down to treatment

- symptomatic and supportive care
- exercise
- supplements
- manipulating mitochondrial fusion, fission, expansion

Of Mice and Men

Tarnopolsky, 2011
PNAS

- POLG Mouse Model
- forced treadmill exercise three times per wk at 15 m/min for 45 min for a period of 5 months. A 5-min warm-up period and a 5-min cool-down period at 8 m/min were included.




HERSHEY'S

Vitamins - What Makes Sense (to me)

CoEnzyme Q10 5 - 20 mg/kg/day ÷ tid

L-Carnitine 30-100 mg/kg/day ÷ tid; 990 mg tid max

Riboflavin 100-600 mg/day qHS

〈 □Lipoic Acid 10 mg/kg/day ÷ bid

Creatine Monohydrate 100 mg/kg/day; 5 gms max

MELAS
L-Arginine 100-300 mg per kg per day
L-Citrulline 100-300 mg per kg per day

Kearn-Sayre Syndrome ?
Folinic Acid 5-50 mg a day


S M T W T F S
The Medicine Shoppe
MAY 17 2006

Take Home Messages

- 1:200 people harbor a pathogenic mutation in mtDNA
    - future generations
    - > 200 pathogenic mutations in the mtDNA
    - 1:5000 people have MELAS (A3243G) disease
- 1:10000 people have a fatal POLG disorder
    - 2% of people harbor one fatal POLG mutation
- there are ~ 1500 genes critical for mitochondrial function and clinical information is known for ~ 40 of them

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DOD 9/4/1994


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