DYSAUTONOMIA INTERNATIONAL

AWARENESS ADVOCACY ADVANCEMENT

The Basics: What Are Mitochondria and Mitochondrial Disease?

What Does It Mean For Dysautonomia?

Richard G. Boles, M.D.
Medical Director, Courtagen Life Sciences, Inc.
Woburn, Massachusetts
Medical Geneticist in Private Practice
Pasadena, California

Dysautonomia International; 18-July, 2015
Herndon, Virginia

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Disclosure: Dr. Boles wears many hats

Dr. Boles is a consultant for Courtagen, which provides diagnostic testing.

- Medical Director of Courtagen Life Sciences Inc.
  - Test development
  - Test interpretation
  - Marketing

Courtagen LIFE SCIENCES, INC.

- Researcher with prior NIH and foundation funding
  - Studying sequence variation that predispose towards functional disease
  - Treatment protocols

Children's Hospital LOS ANGELES We Treat Kids Better

USC UNIVERSITY OF SOUTHERN CALIFORNIA

- Clinician treating patients
  - Interest in functional disease (CVS, autism)
  - Geneticist/pediatrician 20 years at CHLA/USC
  - In private practice since 2014

Mitochondrial and Molecular Medicine

Richard G. Boles, M.D.
Medical Genetics
Pasadena, California

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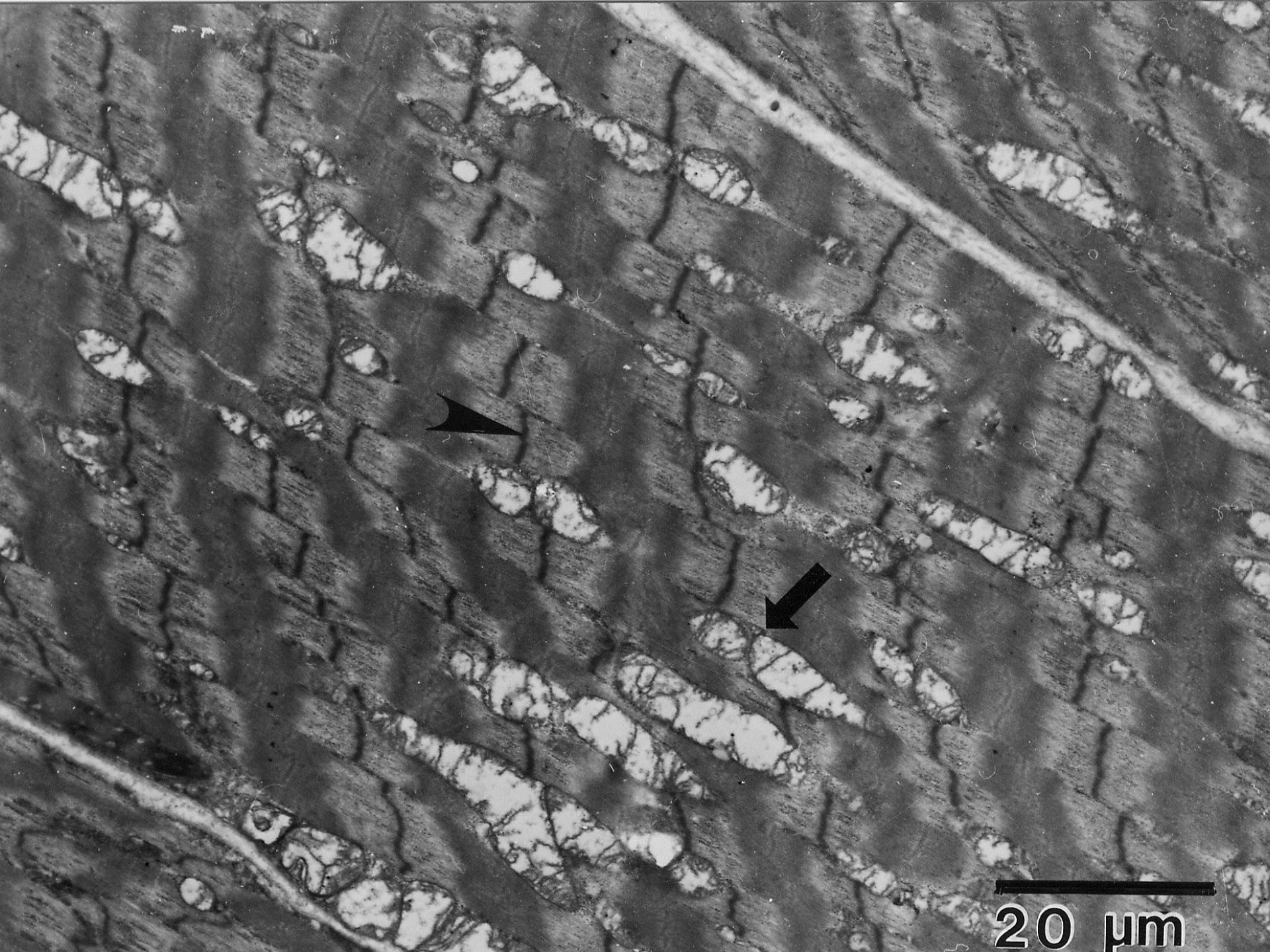
Disclosure: Off-label Indications

There are no approved treatments for mitochondrial disease.

Everything is “off label”


20 µm

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Payton, 15-year-old

- Presented to my clinic at age 11 years.
- Cyclic vomiting syndrome from ages 1-10 years, with 2-day episodes twice a month of nausea, vomiting and lethargy.
- Episodes had morphed into daily migraine.
- Chronic pain throughout her body.
- Chronic fatigue syndrome = chief complaint.
- Substantial bowel dysmotility/IBS

  Multiple admissions for bowel clean-outs.
- Excellent student
- Pedigree: probable maternal inheritance

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TRAP1-Related Disease (T1ReD)
Mitochondrion, 2015

- NextGen sequencing at age 14 years revealed the p.Ile253Val variant in the *TRAP1* gene.
- *TRAP1* encodes a mitochondrial chaperone involved in antioxidant defense.
- This patient is one of 26 unrelated cases identified by Courtagen to date who have previously unidentified disease associated with mutations in the ATPase domain.
- The common feature recognized at present is chronic pain, fatigue and GI dysmotility.
- Tachycardia/palpitations and dizziness may also be common.
- That variant comes from Payton's father, who himself has frequent pain, fatigue and diarrhea.
- In these patients, chronic pain and fatigue improved greatly on aggressive antioxidant therapy.
- On aggressive antioxidant therapy, all manifestations of disease in Payton were substantially improved. Issues remaining included chronic abdominal pain and moderate fatigue. She became functional in life, but still on a shortened school schedule.

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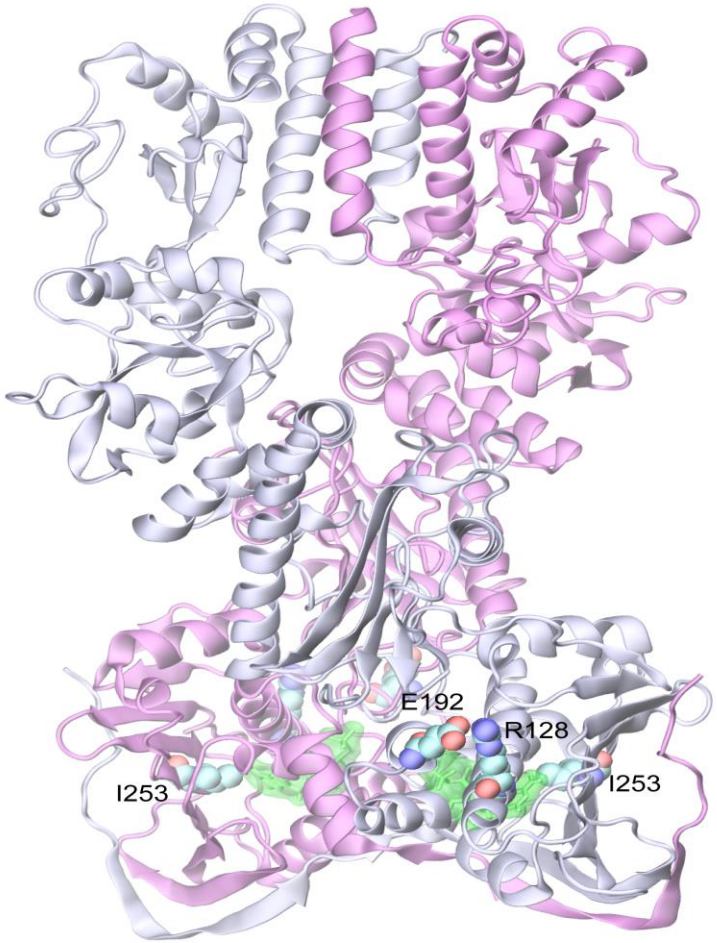
Molecular structure of TRAP1

TRAP1-Related Disease (T1ReD)



- 1. An ATPase domain hydrolyze the energy-rich triphosphate bond of ATP to convert into mechanical work of folding proteins.
- 2. The two homodimers of TRAP1 are shown in grey and pink.
- 2. ATP bound in its pocket is shown in green, in each dimer.
- 3. The “common mutation” p.Ile253Val is labeled in each dimer.
- 4. The “salt bridge” mutations, R128H (p.Arg128His) and E192K (p.Glu192Lys), are labeled in one dimer.

Can we design a therapy that blocks ATP entrance into mutant TRAP1, but not normal TRAP1?

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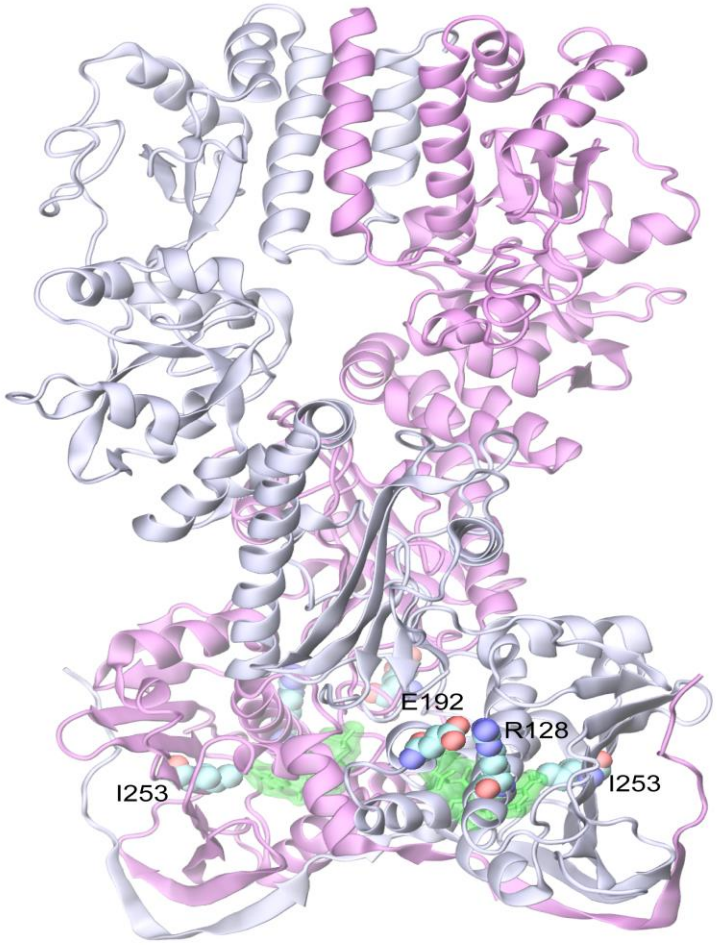
Molecular structure of TRAP1

TRAP1-Related Disease (T1ReD)



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Can we design a therapy that blocks ATP entrance into mutant TRAP1, but not normal TRAP1?
Computer modeling was performed based on the human TRAP1 crystal structure by Jeffrey Skolnick at the Georgia Institute of Technology.

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What Are Mitochondria?

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What Are Mitochondria?

Ask the Wookieepedia!

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What Are Mitochondria?

Midi-chlorians were intelligent microscopic life forms that lived symbiotically inside the cells of all living things.

"Without the midi-chlorians, life could not exist, and we would have no knowledge of the Force. They continually speak to us, telling us the will of the Force." - Qui-Gon Jinn

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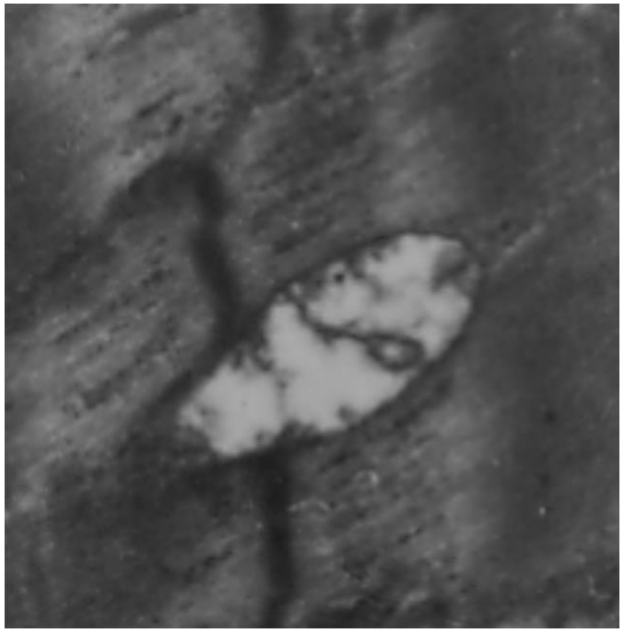
What Are Mitochondria?



Don’t they look similar?

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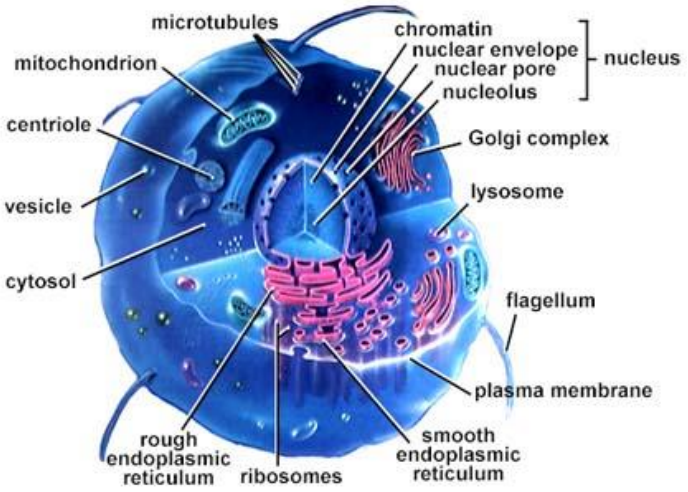
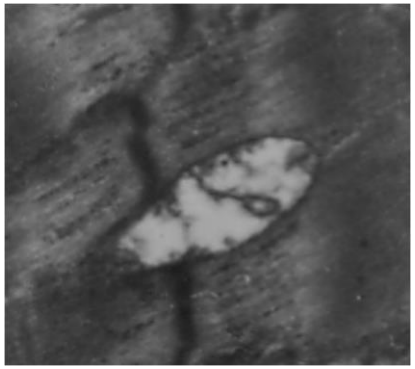
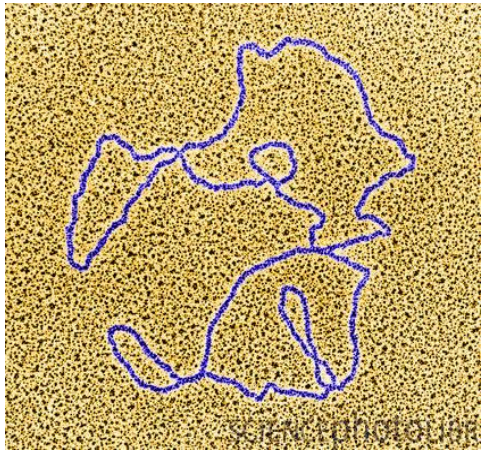
Mitochondrial Genetics
The Basics





Mitochondrial DNA

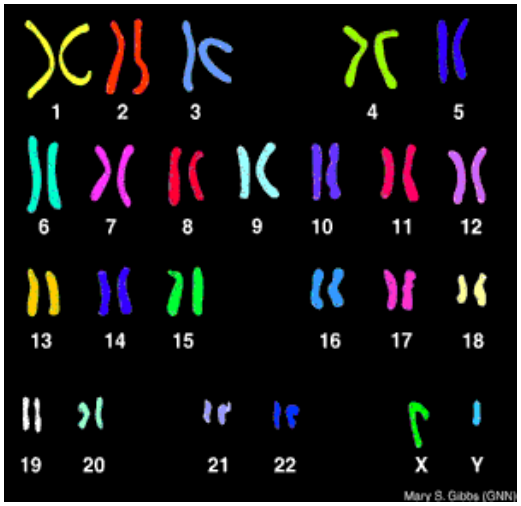


37 genes

16,000 base pairs

- Maternal inheritance

Nuclear DNA



~22,000 genes

3,000,000,000 base pairs

1,013 genes encode mitochondrial proteins

- Autosomal recessive
- Autosomal dominant
- X-linked

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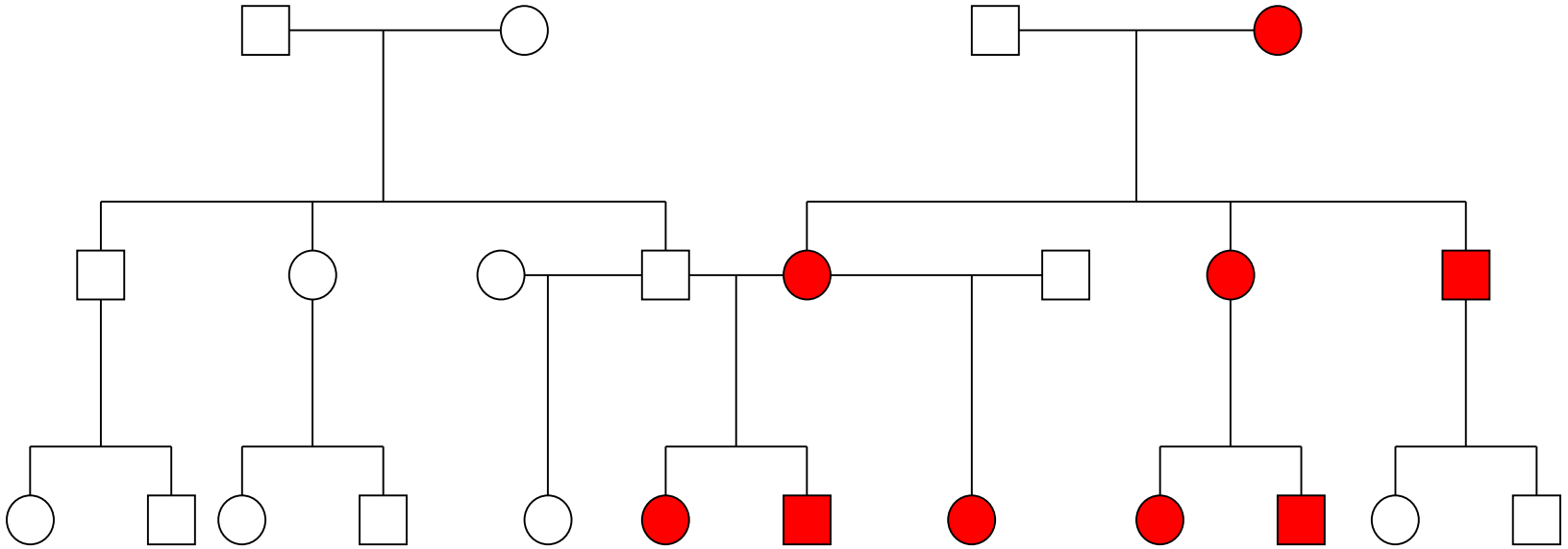
AWARENESS ADVOCACY ADVANCEMENT

Maternal Inheritance



mtDNA is inherited exclusively from the mother.
There is no recombination.

Thus, all relatives with red symbols have exactly the same mtDNA sequence, in the absence of a new mutation.

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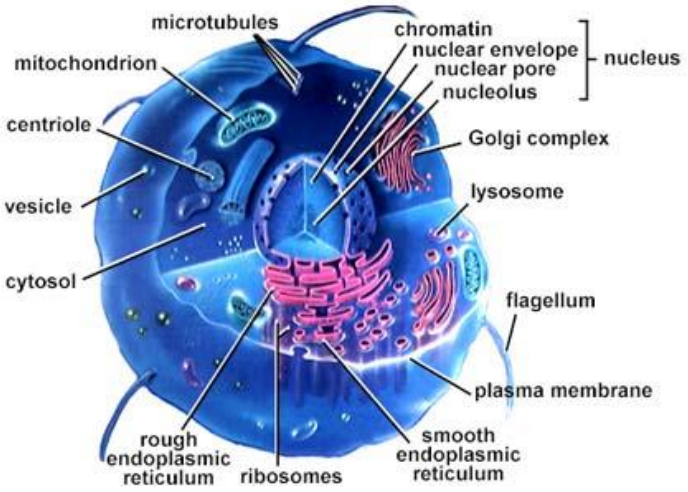
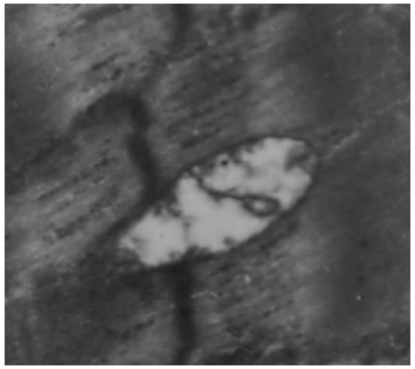
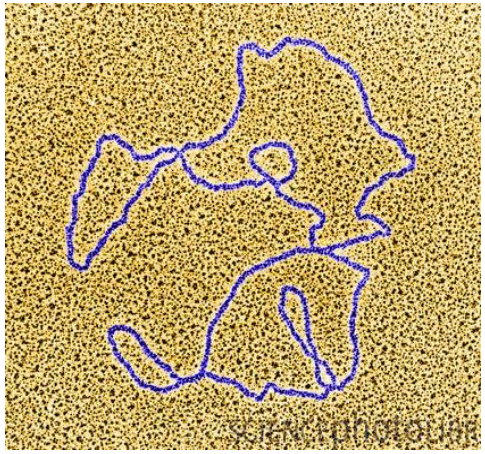
Mitochondrial Genetics
The Basics





Mitochondrial DNA



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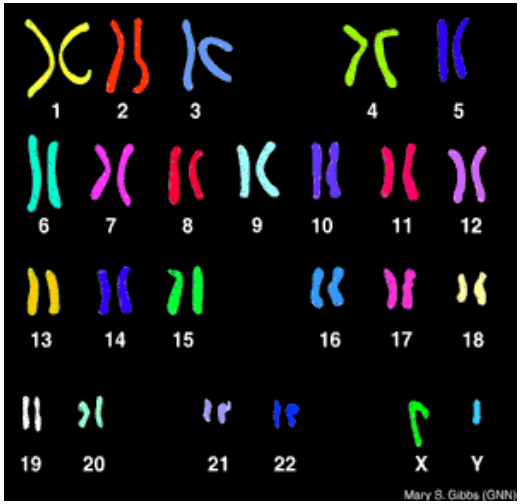
- Maternal inheritance

Nuclear DNA



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3,000,000,000 base pairs
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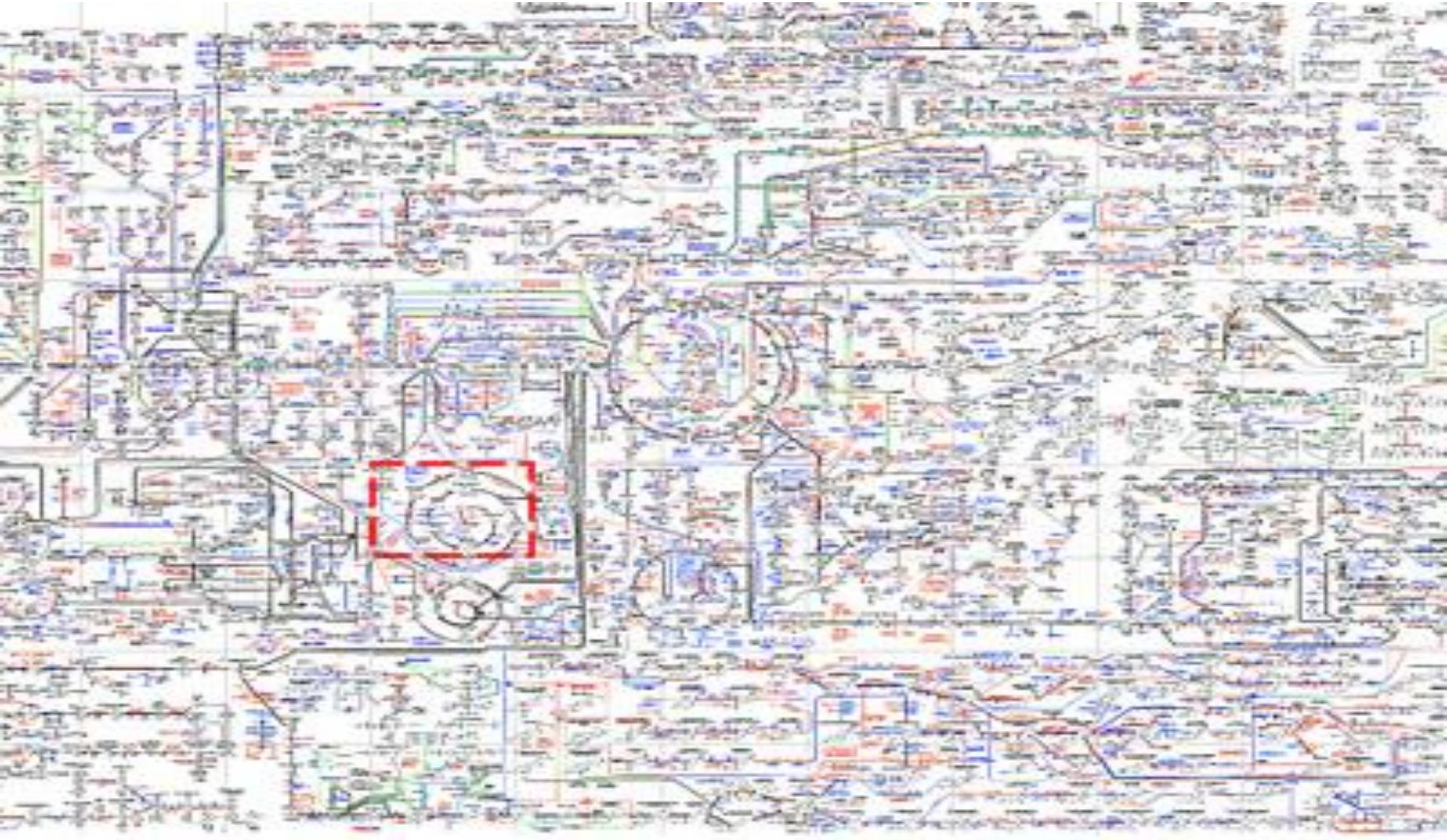
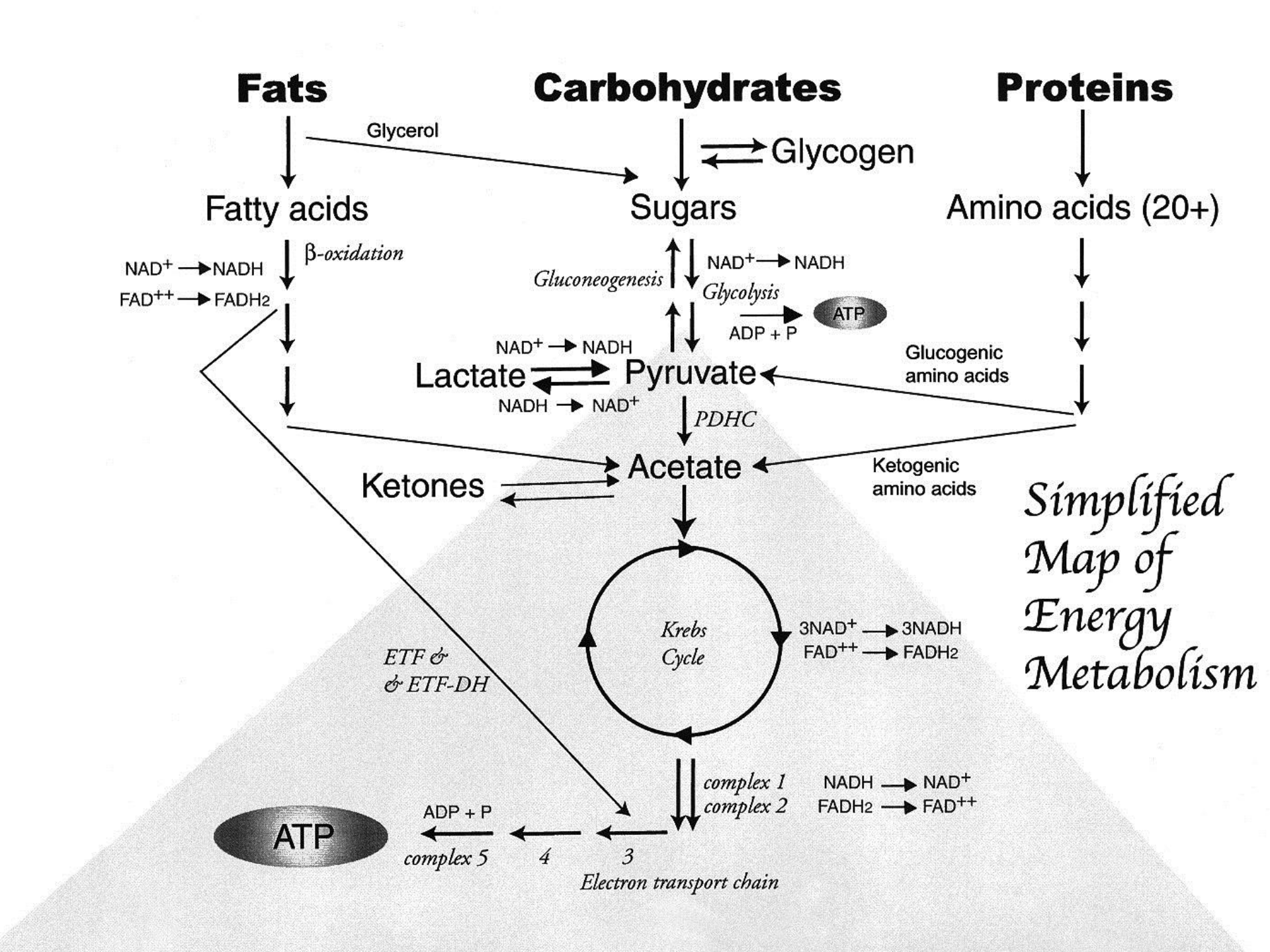
Metabolic Pathways




Fats
Carbohydrates
Proteins
Glycerol
Glycogen
Fatty acids
Sugars
Amino acids (20+)
β-oxidation
NAD+ → NADH
FAD++ → FADH2
Gluconeogenesis
Glycolysis
NAD+ → NADH
ATP
ADP + P
NAD+ → NADH
Lactate
Pyruvate
NADH → NAD+
Glucogenic amino acids
PDHC
Acetate
Ketones
Ketogenic amino acids
Krebs Cycle
3NAD+ → 3NADH
FAD++ → FADH2
ETF & & ETF-DH
complex 1
complex 2
NADH → NAD+
FADH2 → FAD++
ATP
ADP + P
complex 5
4
3
Electron transport chain
Simplified Map of Energy Metabolism

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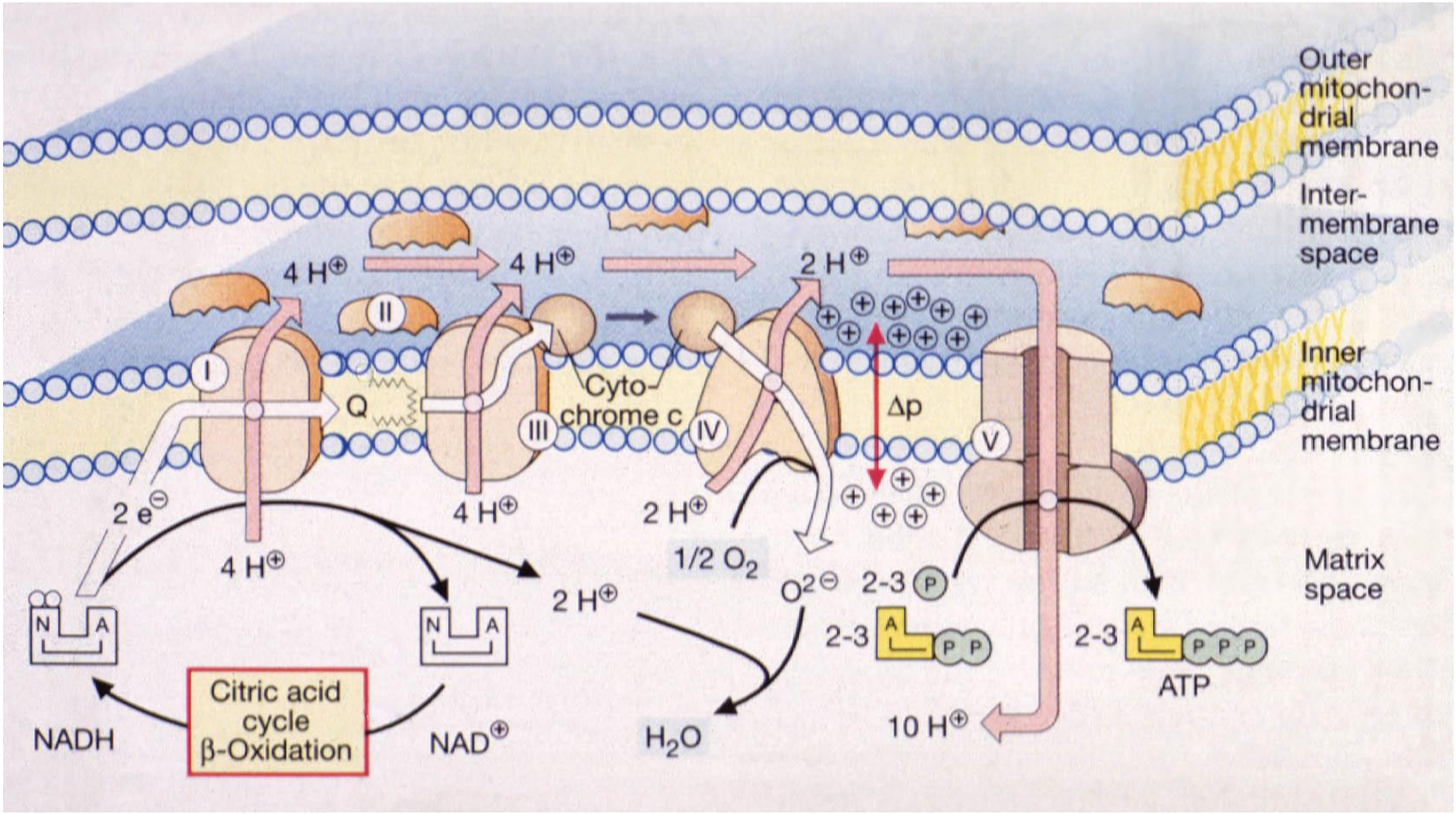
Electron Transport Chain



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What Is Mitochondrial Disease?

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What Is Mitochondrial Disease?

Genetic defects affecting the body's ability to make ATP (energy) are termed "mitochondrial disorders"

Mutations can be in the nuclear DNA (chromosomes) or the mitochondrial DNA (mtDNA)

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What Is Mitochondrial Disease?

crazy20nancy20straight20jacket.jpg

These conditions are genetic, although many families have only one affected person. Even when familial, with every relative affected in a very different manner, the connections are difficult to see.

Signs and symptoms come and go to different parts of the body depending on the energy flux of each tissue in each minute. Patients are often not believed, or thought to be "psychiatric".

In addition to the 37 genes on the mtDNA, there are at least another 1,088 genes in the nucleus that encode proteins which are imported into the mitochondria.

Many patients do NOT have a real diagnosis!

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What Is Mitochondrial Dysfunction?

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What Is Mitochondrial Dysfunction?

"Mitochondrial Dysfunction" =
mitochondria are not working properly

Can be "primary" due to an underlying defect within the mitochondria = "mitochondrial disease"

Can be "secondary" due to an underlying defect outside the mitochondria = "?????????"

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What Have You Learned?

- Mitochondria are derived from ancient bacterial symbiotes that live within our cells.
- They have maintained some of the original bacterial DNA.
  - This mtDNA is inherited only from the mother.
  - Mutations in the mtDNA can cause mitochondrial disease and dysfunction.
- Most of the DNA that codes for mitochondrial proteins in is the nucleus
  - Most of that DNA comes equally from both parents.
  - Mutations in those genes can cause mitochondrial disease and dysfunction.
- Many diseases that derive from defects outside of the mitochondria can result in secondary mitochondrial dysfunction.
- Mitochondria make the vast majority of the energy that the cell uses.
  - All cells need energy – for nearly everything they do.
  - Thus, mitochondrial disease can affect almost any part of the body, and contribute towards almost every condition/disease.

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What is Mitochondrial Disease?

How can you stand here and tell us that mitochondrial disease can underlie just about any disease!

What is Mitochondrial Disease?

How can you stand here and tell us that mitochondrial disease can underlie just about any disease!

Are you a quack?

Energy!

mad-scientist-lightning.jpg

UNITED MITOCHONDRIAL DISEASE FOUNDATION®
HOPE. ENERGY. LIFE.

Mitochondrial Medicine
The Spectrum of Mito

Brain
- Developmental delays
- Dementia
- Neuro-psychiatric disturbances
- Migraines
- Autistic Features
- Mental retardation
- Seizures
- Atypical cerebral palsy
- Strokes

Nerves
- Weakness (may be intermittent)
- Absent reflexes
- Fainting
- Neuropathic pain
- Dysautonomia - temperature instability

Muscles
- Weakness
- Cramping
- Gastrointestinal problems
- Dysmotility
- Irritable bowel syndrome
- Hypotonia
- Muscle pain
- Gastroesophogeal reflux
- Diarrhea or constipation
- Pseudo-obstruction

Kidneys
- Renal tubular acidosis or wasting

Heart
- Cardiac conduction defects (heart blocks)
- Cardiomyopathy

Liver
- Hypoglycemia (low blood sugar)
- Liver failure

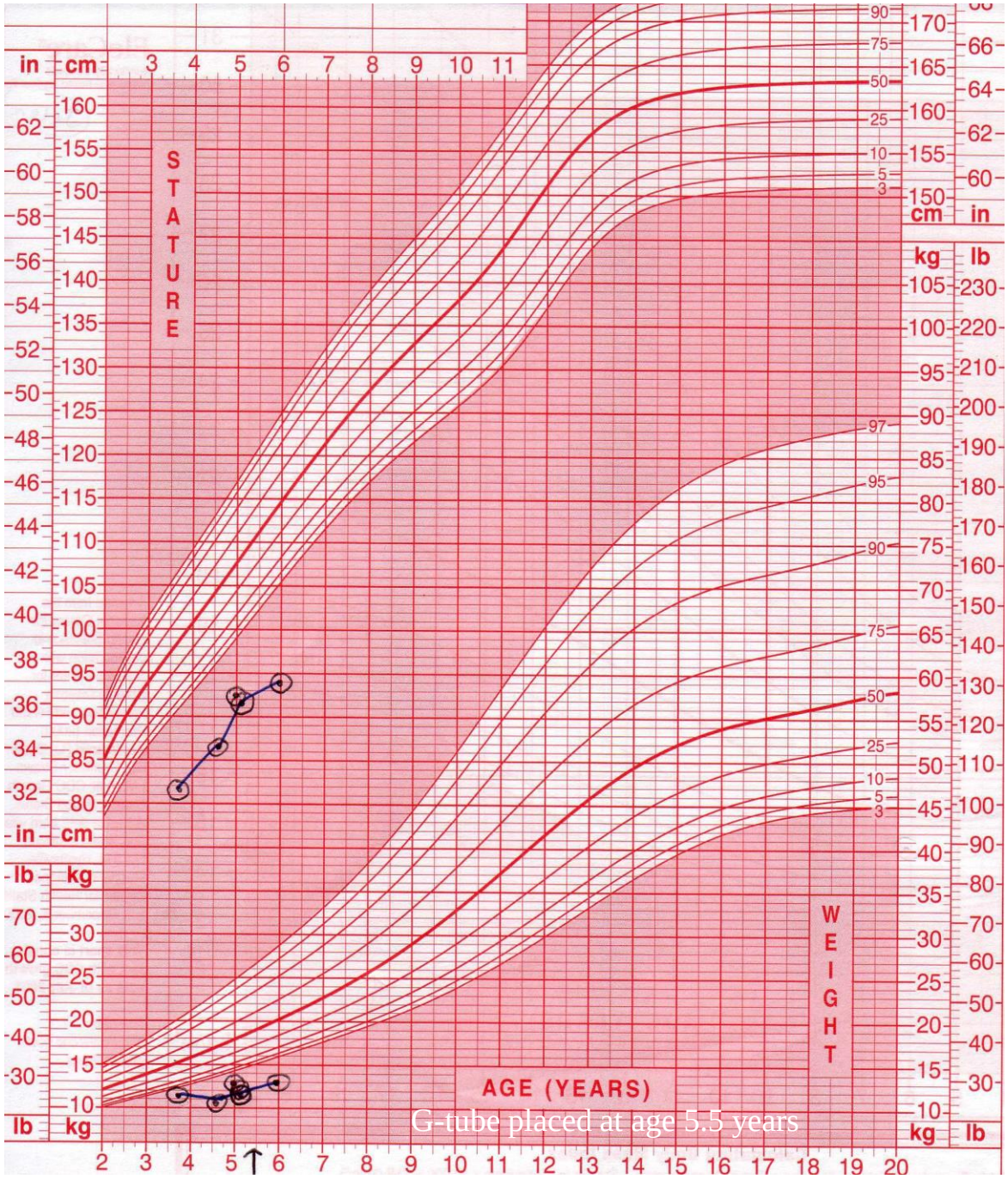
Ears & Eyes
- Visual loss and blindness
- Ptosis
- Ophthalmoplegia
- Optic atrophy
- Hearing loss and deafness
- Acquired strabismus
- Retinitis pigmentosa

Pancreas & other glands
- Diabetes and exocrine pancreatic failure (inability to make digestive enzymes)
- Parathyroid failure (low calcium)

Systemic
- Failure to gain weight
- Fatigue
- Unexplained vomiting
- Short stature
- Respiratory problems

Helen:

Cyclic vomiting syndrome
Ocular myopathy (ptosis and ophthalmoplegia)
Pigmentary retinopathy
Mild developmental delay
Ataxia
Hypotonia
Muscle weakness
Exercise intolerance
Severe GI dysmotility
Episodic leg pain
Photophobia
Growth retardation



Large mtDNA Deletion Case Growth Curves

Weight is paralleling the curves.

Weight is appropriate for height.

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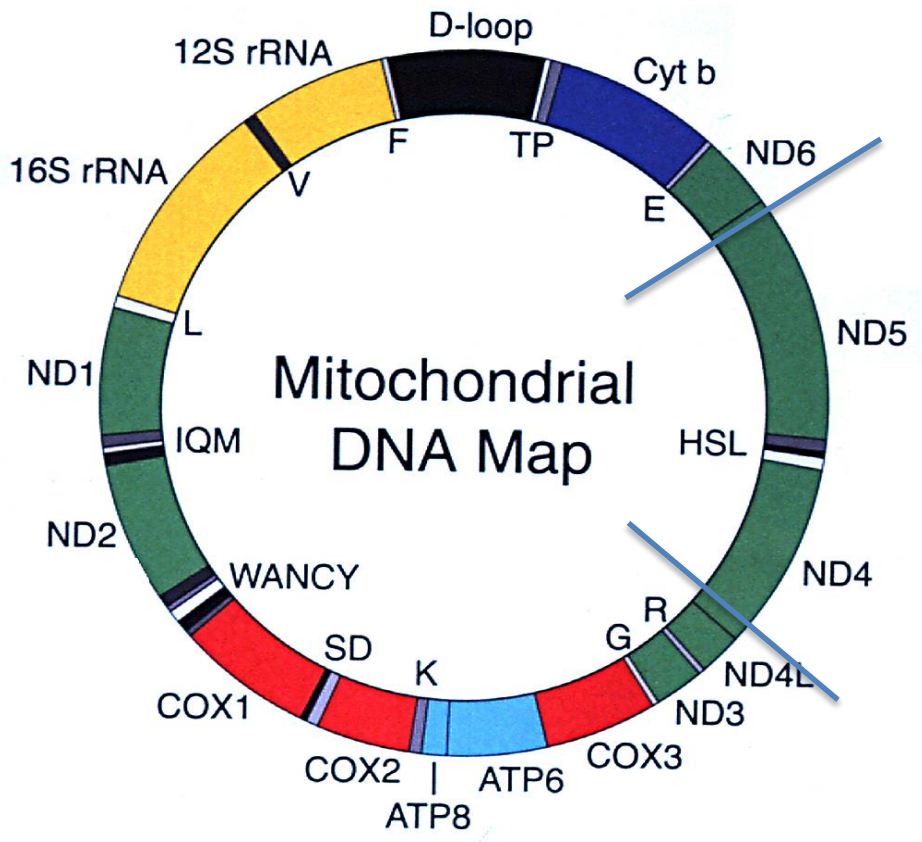

A case of Kearns-Sayre syndrome:

The 3K base-pairs between the blue lines is deleted in a proportion of the mtDNA.

The deleted molecules are smaller, and replicate faster, causing disease progression.

Prognosis: progressive multi-system failure leading to death.

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What Is Functional Disease?

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What Is Functional Disease?

A poem by a 14-year-old patient

I never know when its going to come back
This fatigue is an internal attack
It so easily cripples me
Only no one can see

Its so hard when you easily tire
And everyone around you thinks your lazy and a liar
They cant see so they don't know
I know in my heart its real though

Its a relief to get the answer and know you're not crazy
You can finally prove you're not just lazy
Its still not easy and never will be
But maybe some day the world will see

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20 "Functional" Disorders:

- Attention deficit hyperactivity disorder
- Anxiety disorder
- Autistic spectrum disorders
- Chronic fatigue syndrome
- Complex regional pain syndrome
- Cyclic vomiting syndrome
- Depression (MDD)
- Fibromyalgia
- Functional abdominal pain
- Interstitial cystitis
- Insomnia (chronic, severe)
- Irritable bowel syndrome
- Migraine
- Panic disorder
- Post-traumatic stress disorder
- Postural orthostatic tachycardia syndrome
- Restless legs syndrome
- Temporomandibular disorder
- Tinnitus
- Vulvovaginitis syndrome

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Comorbidity: Functional Conditions Are Often Found Together

- 44% of patients with interstitial cystitis also have symptoms suggestive of irritable bowel syndrome (IBS) (v. 12% of controls).
- 59% of patients with cyclic vomiting syndrome met the standardized questionnaire criteria for a generalized anxiety disorder.
- 67% of migraineurs fulfilled criteria for chronic fatigue syndrome.
- 75% of patients with cyclic vomiting syndrome are projected to develop migraine by age 18.
- 20% to 80% of patients with temporomandibular disorders suffer from additional chronic pain disorders such as headache, low back pain, fibromyalgia, and irritable bowel syndrome.

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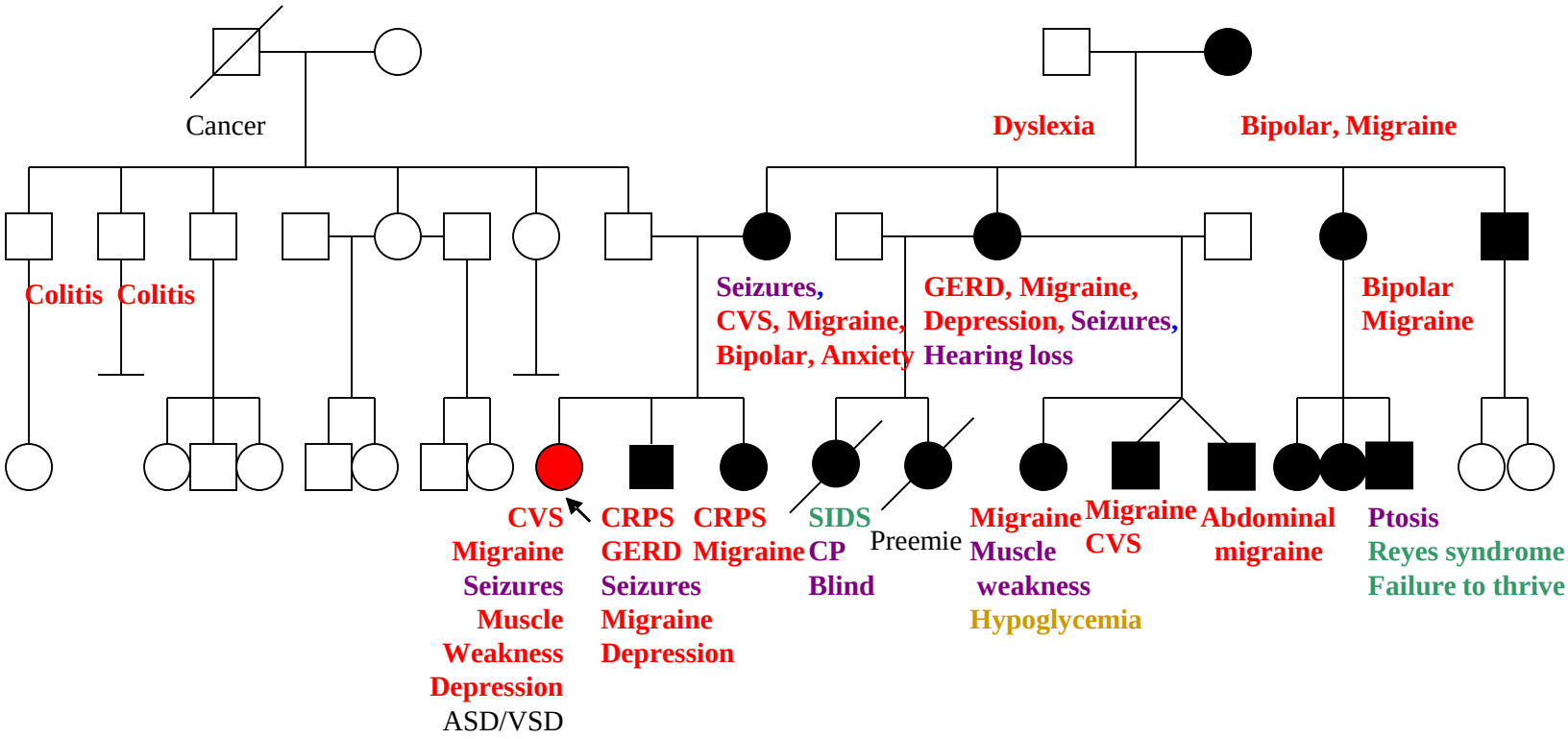
Maternal Inheritance of Functional Disorders - 1



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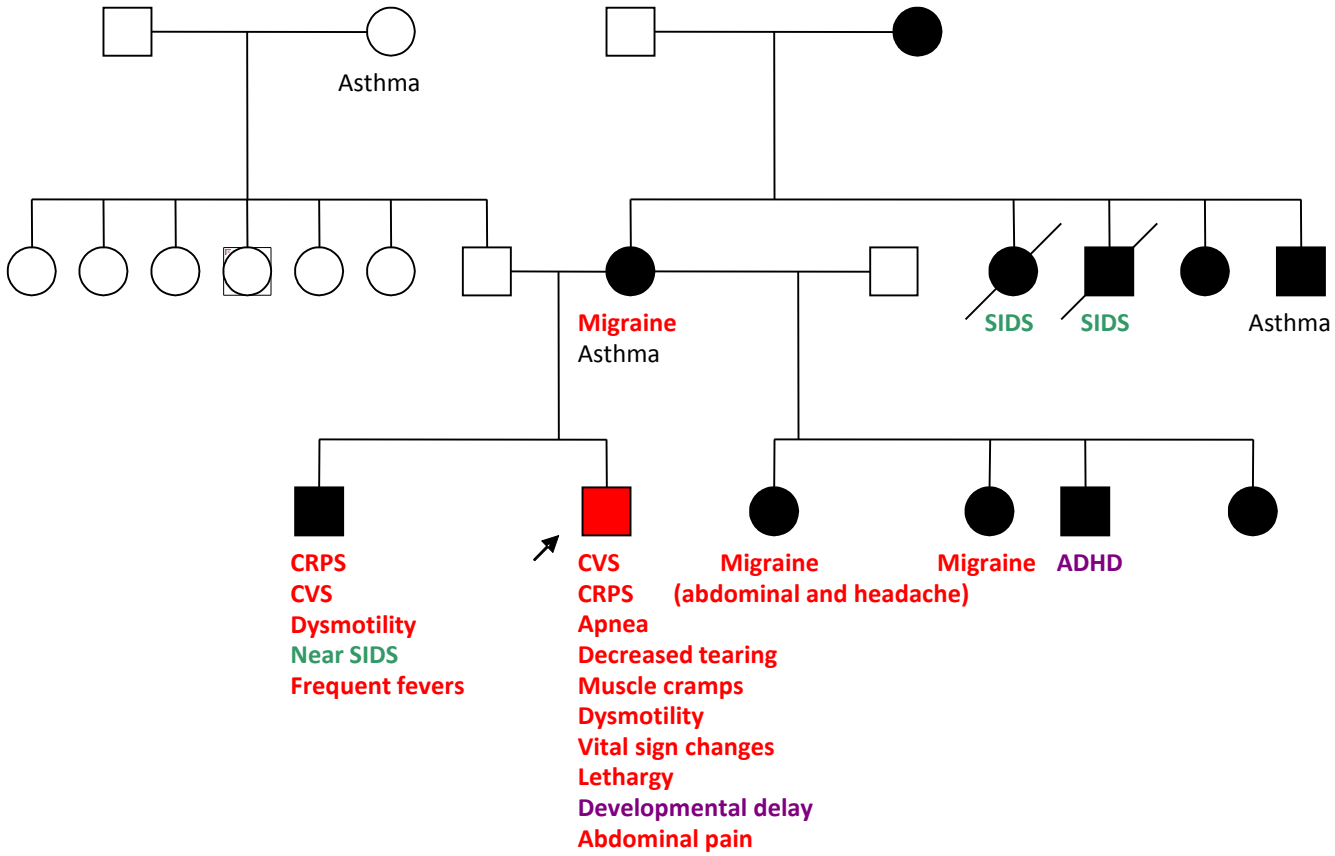
Maternal Inheritance of Functional Disorders - 2



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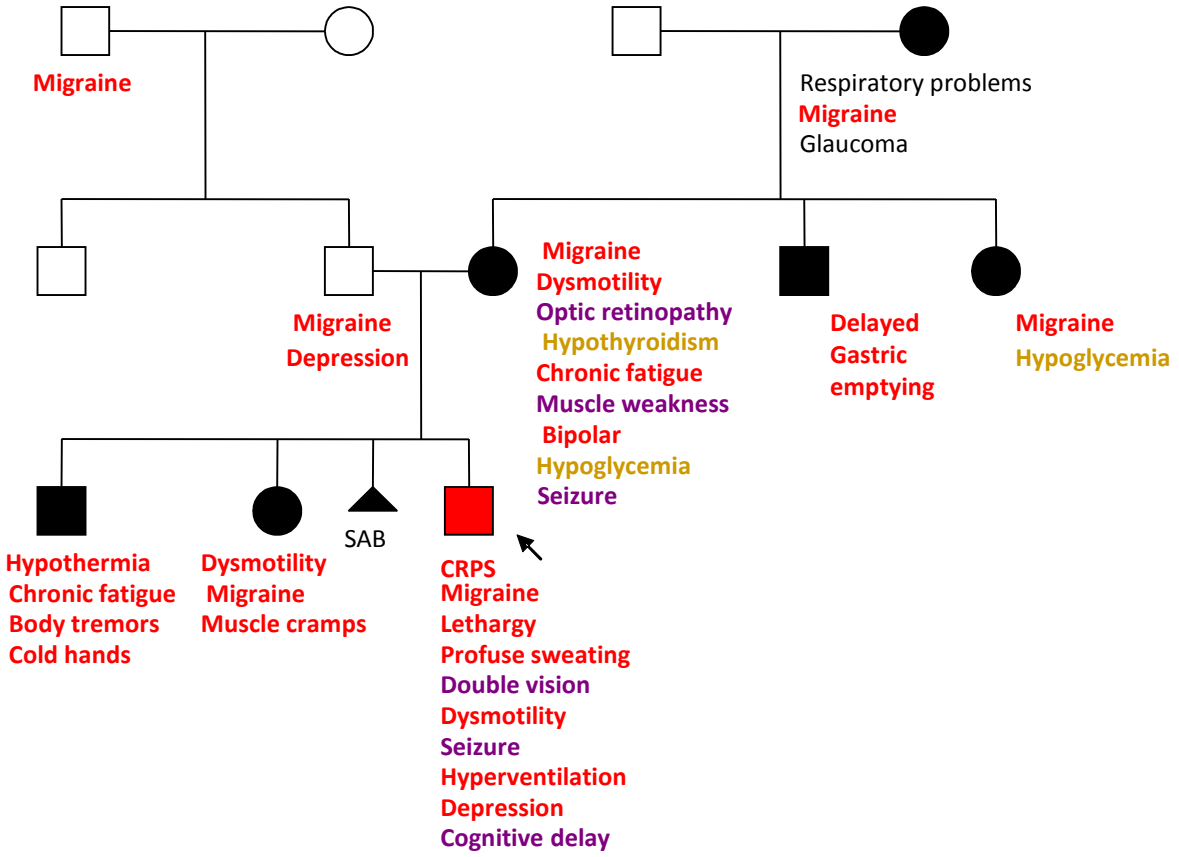
Maternal Inheritance of Functional Disorders - 3



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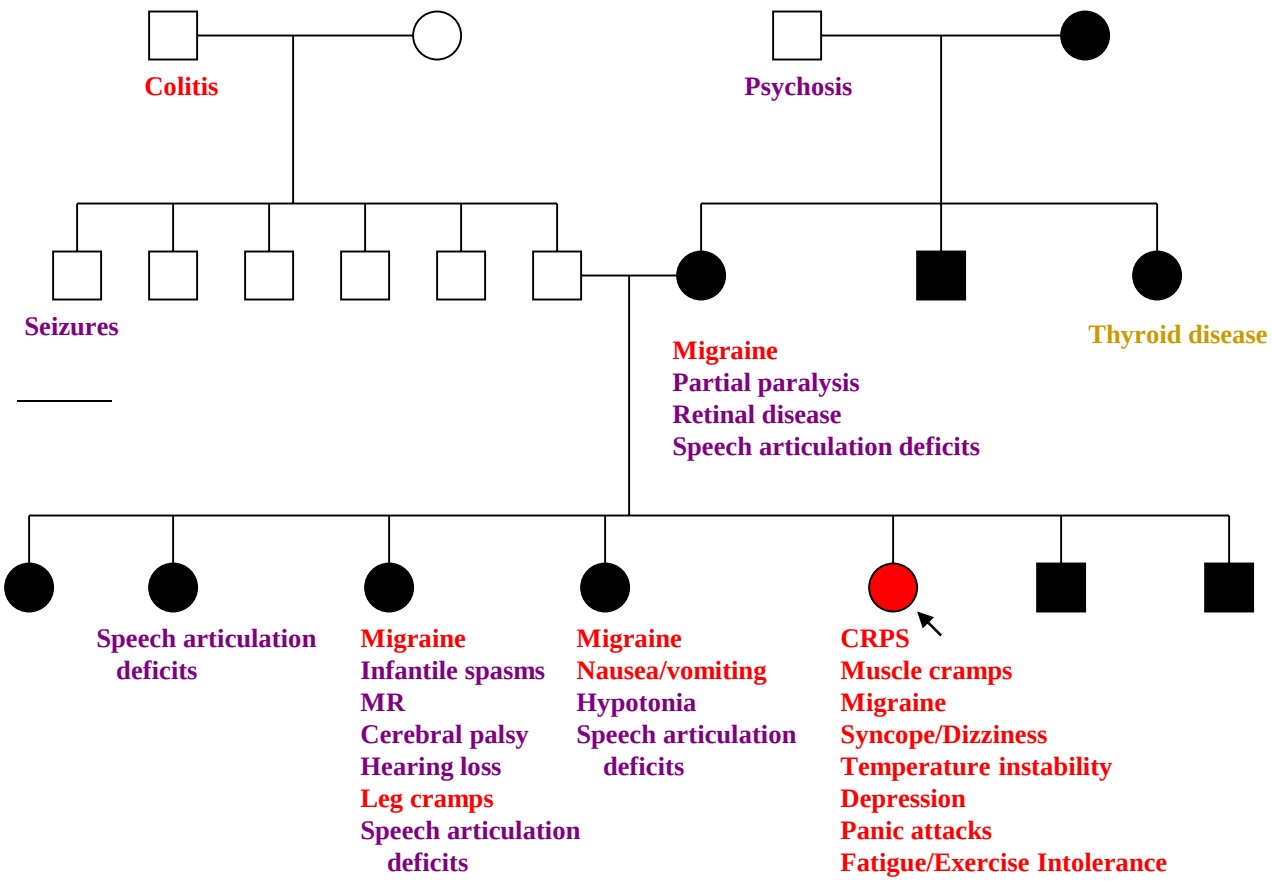
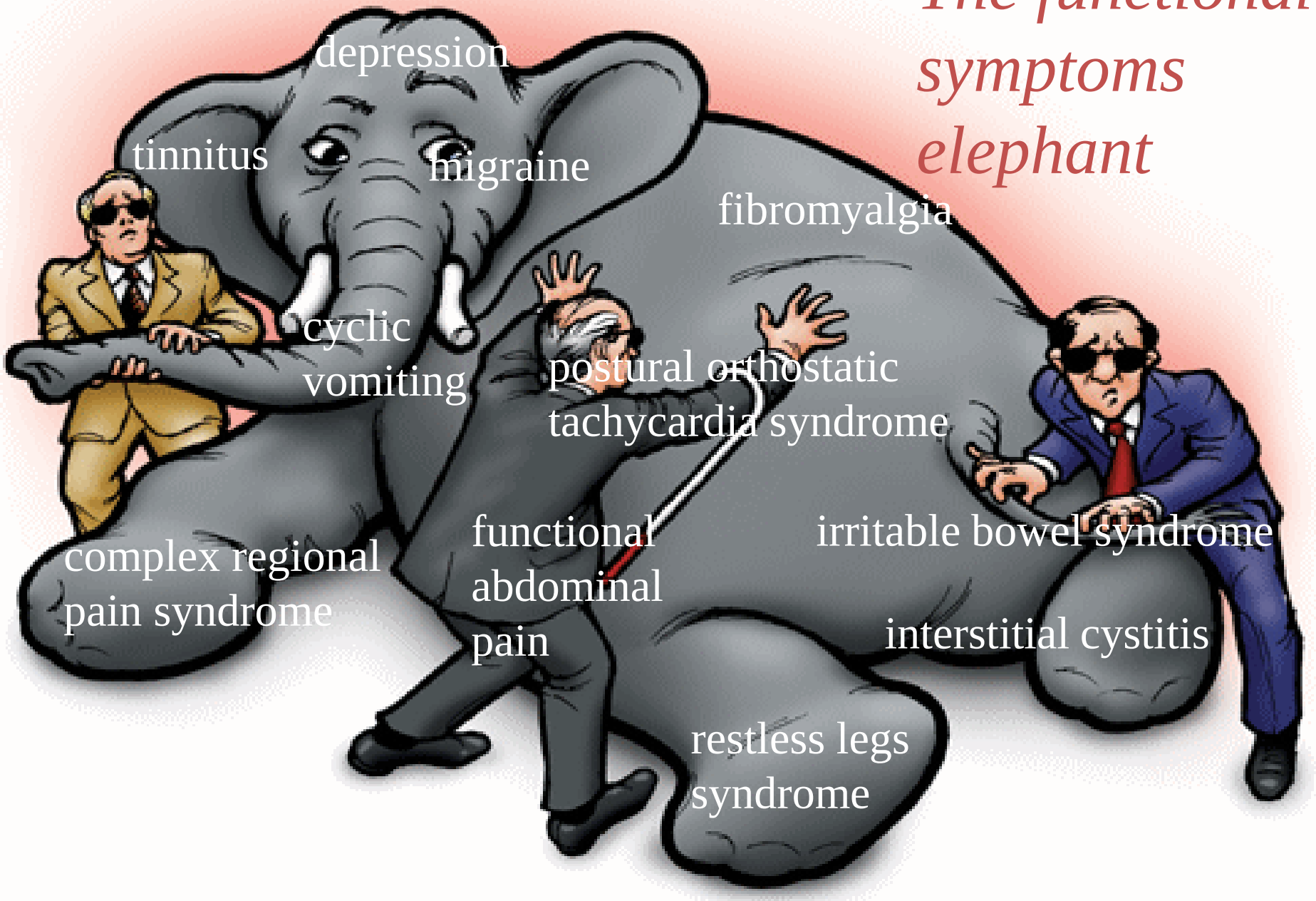
Maternal Inheritance of Functional Disorders - 4



Gardner
Boles 2006

The functional symptoms elephant



The elephant is lying down due to chronic fatigue

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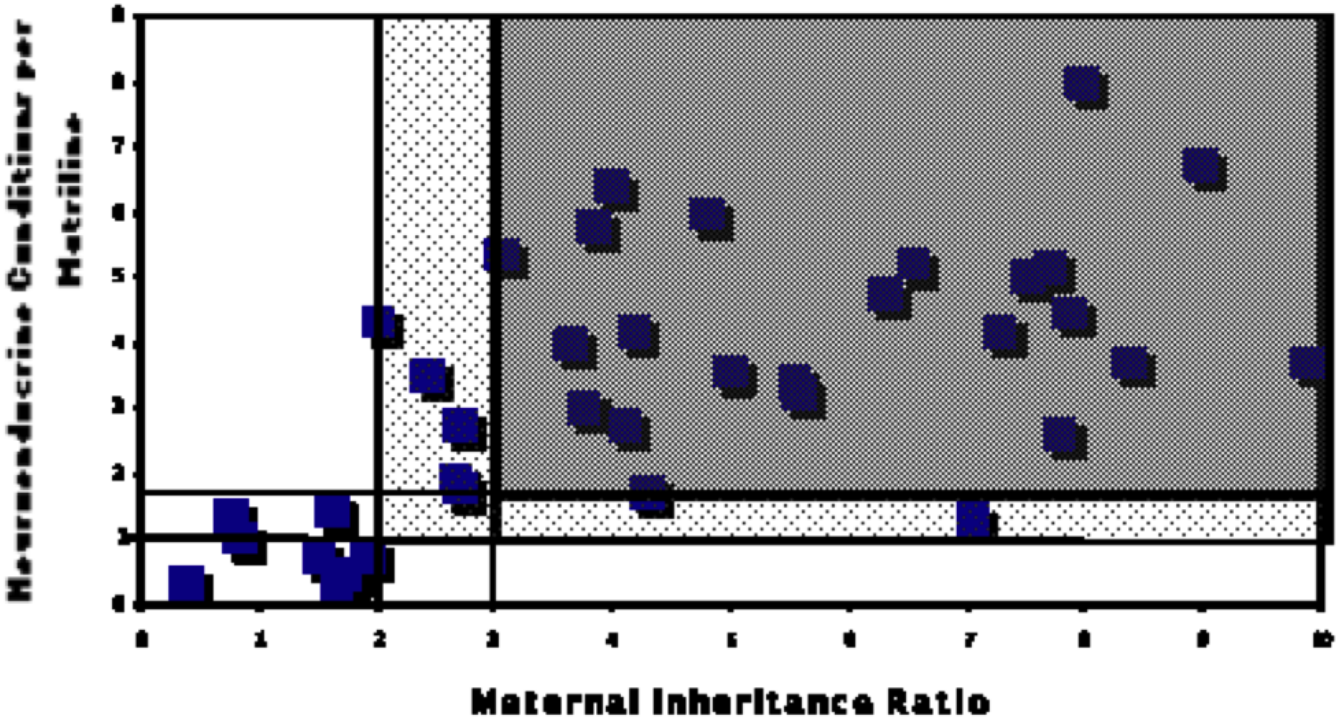
Quantitative Pedigree Analysis In Cyclic Vomiting Syndrome



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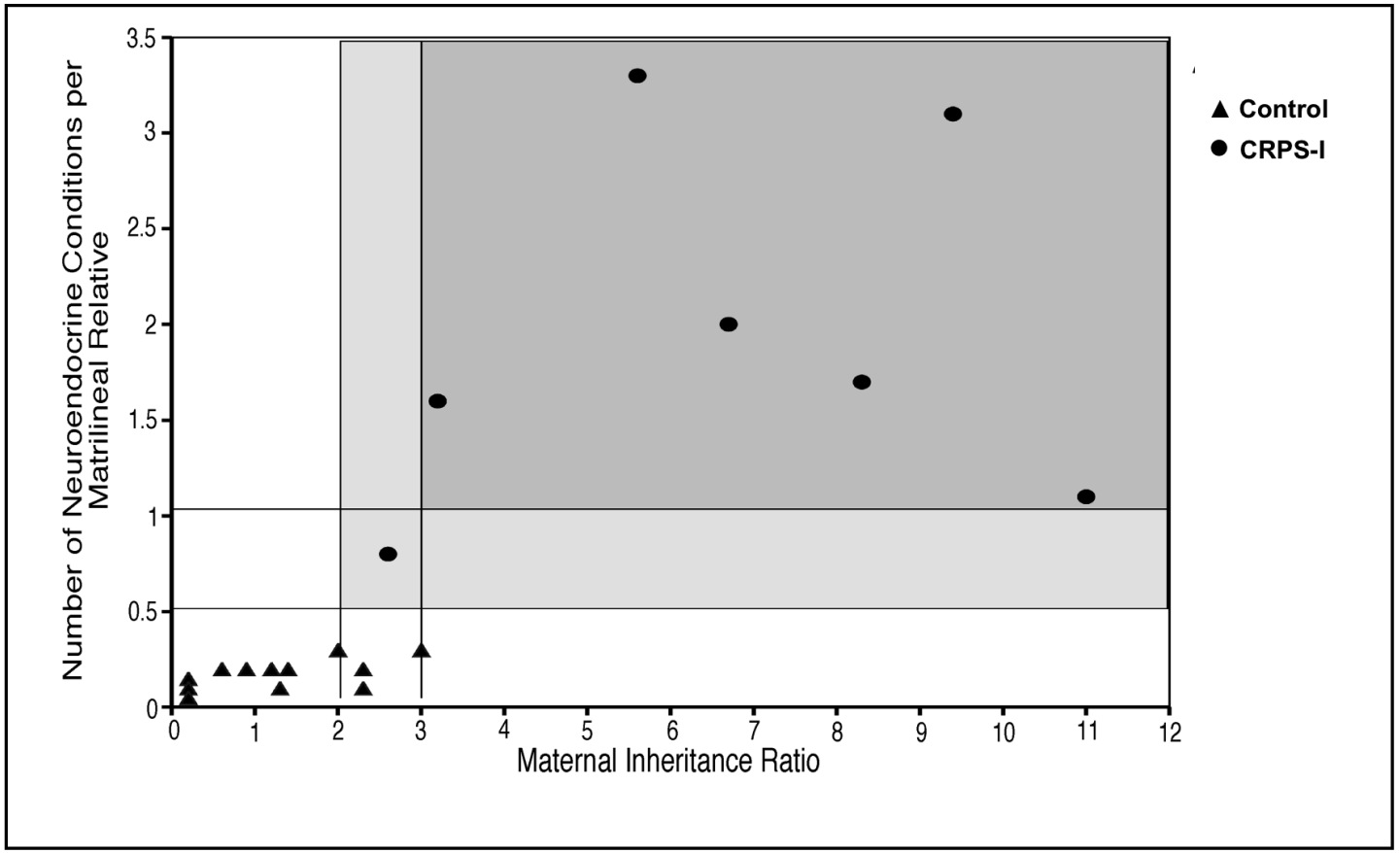
Quantitative Pedigree Analysis In Complex Regional Pain Syndrome

Figure 2: Labeling of pedigrees as "probable maternal inheritance," "probable non-maternal inheritance," or "indeterminate."



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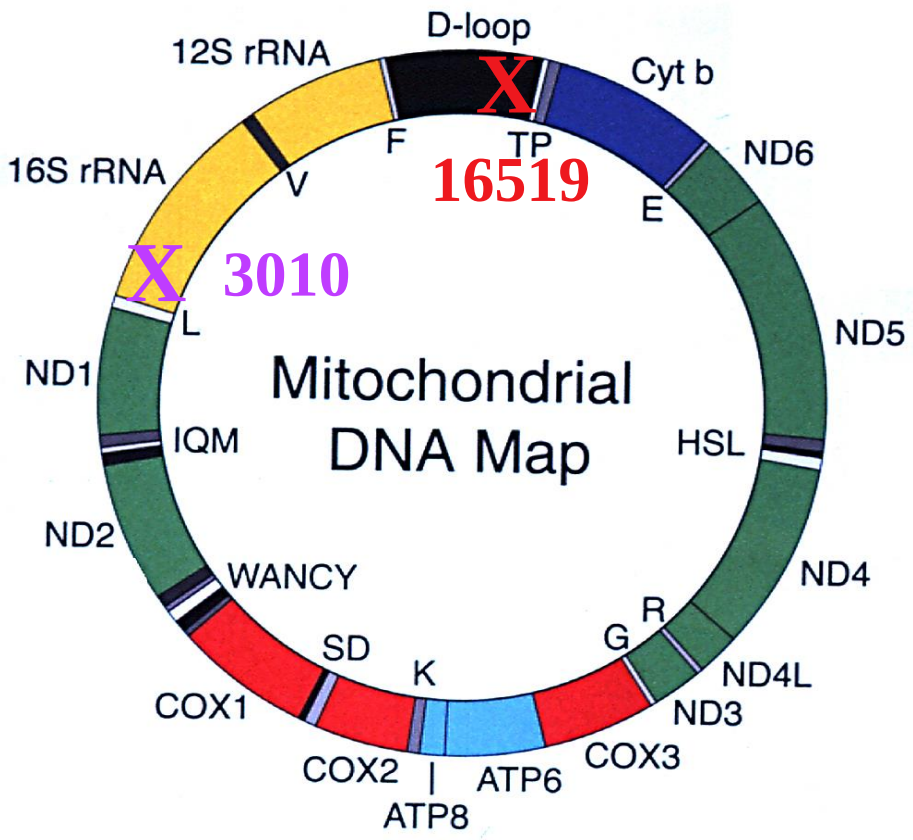
Functional Disorder-Associated mtDNA Polymorphisms



16519 C>T

mtDNA control region

3010 G>A

16S-ribosomal RNA gene

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Cyclic Vomiting and Migraine Prevalence of Two mtDNA Common Variants in Haplogroup H Individuals With Functional Disorders

	Cyclic Vomit Syndr.	Odds Ratio (95% C.I.)	Migraine w/o Aura	Odds Ratio (95% C.I.)	Ctrl
16519T	21/30 70%	6.2 (2.7-14)	58/112 52%	3.6 (2.2-5.9)	63/231 27%
3010A	9/30 30%	N/A	37/112 33%	N/A	143/444 32%
3010A among pts with 16519T	6/24 29%	**17** (2-156)	15/58 26%	**15** (1.9-117)	1/63 1.6%

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Chronic Fatigue Syndrome The 3010A mtDNA Variant Predicts a Several-fold Increase in Functional Symptoms.

	Headache	Fainting or Dizziness	Muscle Pain	Muscle Weakness	Sleep Problems	Numbness or Tingling
3010A	14/21 67%	11/21 52%	19/21 90%	17/21 81%	19/22 86%	12/21 57%
3010G	8/25 32%	5/28 18%	16/28 57%	17/28 61%	13/27 48%	6/24 25%
Chi Square	P = 0.04	P = 0.02	P = 0.03	*P = 0.22*	P = 0.01	*P = 0.06*
Odds Ratio (95% C.I.)	**4.0** (1.1-18)	**4.7** (1.2-23)	**5.9** (1.2-54)	NA	**6.0** (1.4-38)	**3.7** (0.95-18)
T-test	P =	*P = 0.06*	P =	P = 0.03	P =	P = 0.03

What Have You Learned?

- Functional disease:
  - is very common.
  - can affect nearly any part of the body.
  - can be mild to disabling.
  - is often clustered: with many functional conditions in the same patient.
  - is often present in a maternal inheritance pattern.
  - can be associated by specific mtDNA variants

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- In addition, functional disease:
  - responds to the same therapies (e.g. amitriptyline, SSRIs, coenzyme Q10).
  - Is related to dysautonomia.
  - may actually be different manifestations of a single disease.

DYSAUTONOMIA INTERNATIONAL

AWARENESS ADVOCACY ADVANCEMENT

Karl, age 27 years
Abdominal migraine

- Presented with cyclic episodes of abdominal pain, nausea, vomiting and pallor.
- Episodes became very frequent and coalesced to near-continuous.
- Status-post cholecystectomy and appendectomy
- On narcotics, fully disabled, and labeled as a drug addict
- Other issues: migraine headaches, fatigue, GERD, anxiety
- Seen in my clinic at age 23 and placed on amitriptyline, coenzyme Q10 and L-carnitine. Initial success with only rare episodes.
- Stopped treatment, and at age 26 was refractory to above therapy, including episodes every 4 to 7 days for several hours; again disabled. Had 10-15 ER visits in 5 months.
- Family history is negative.

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- Stopped treatment, and at age 26 was refractory to above therapy, including episodes every 4 to 7 days for several hours; again disabled. Had 10-15 ER visits in 5 months.
- nucSEEK sequencing revealed 3 known mutations in the *RYR2* gene.
- The patient was place on propranolol.
- Dramatic improvement with the resolution of episodes.

RYR2

Neurogastroenterology and Motility, 2015

- Ryanodine receptor 2
- Encodes a stress-induced calcium channel across the endoplasmic reticulum
- Links with VDAC on the outer mitochondrial membrane to link ER directly with mitochondria
- Dominant mutations are associated with adrenergic-triggered arrhythmia (often fatal) and right-sided cardiomyopathy
- Channel also present in neurons
- Highly-conserved variants are associated with cyclic vomiting
- Have “functional triad” as well – common in CVS
- All are VERY nervous people, with stress-triggered disease
- Disease responds favorably to beta blockade (propranolol)

DYSAUTONOMIA INTERNATIONAL

AWARENESS ADVOCACY ADVANCEMENT

RYR2 variants predispose towards many of the same functional conditions *Neurogastroenterology and Motility*, 2015

Patient	Variant	Selected Functional Co-morbidities*	Control	Variant
1	p.Ser1400Gly	Fatigue	1	p.Arg1119His
2	p.Ser1400Gly, p.Cys2559Tyr	Chronic pain, GI dysmotility	2	p.Gly2145Arg
3	p.Ser1400Gly	GI dysmotility	3	p.Gly1885Glu
4	p.Ser1400Gly	Chronic pain, fatigue, GI dysmotility		
5	p.Ser1400Gly	Chronic pain, fatigue, GI dysmotility		
6	p.Ser1400Gly	Chronic pain, fatigue, GI dysmotility		
7	p.Gly1885Glu	Chronic pain, fatigue, GI dysmotility		
8	p.Gly1885Glu	Chronic pain		
9	p.Gly1885Glu	Chronic pain, GI dysmotility		
10	p.Arg3506Ter	Chronic pain, fatigue		
11	p.Asn4736Asp, p.Ile1925Thr,	Chronic pain, fatigue, GI dysmotility		
12	p.Ile2721Thr	Chronic pain, fatigue, GI dysmotility		
13	p.Met1564Ile	Chronic pain, fatigue		
14	p.Arg1051Cys	Fatigue		
15	p.Ile217Val	Fatigue, GI dysmotility		
16	p.Phe4022Tyr	Fatigue		
17	p.Ala1136Val	Chronic pain, fatigue, GI dysmotility		
18	p.Ala1136Val	Fatigue		

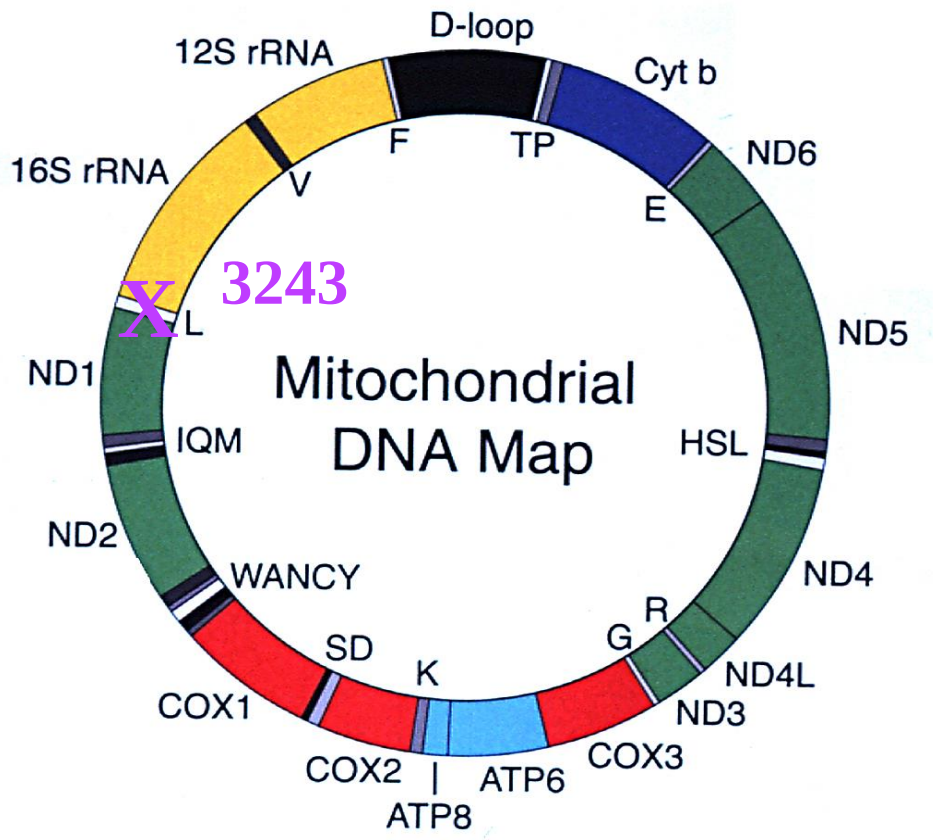
Cyclic vomiting syndrome:
18/75 (24%) subjects vs 3/60 (5%)
Of controls have well conserved *RYR2* variants.
Odds ratio 6.0 (95% C.I 1.7-22)
P = 0.0018


SUGAR
BABIES
09/28/2006

DYSAUTONOMIA INTERNATIONAL

AWARENESS ADVOCACY ADVANCEMENT

MELAS: Mitochondrial myopathy, Encephalopathy, Lactic Acidosis and Stroke-like episodes



3243 A>G

Transfer RNA gene for leucine (UUR)

Brain disease
Muscle disease

Malignant migraine >
Stroke-like episodes >
Stroke >
Disability and death

DYSAUTONOMIA INTERNATIONAL

AWARENESS ADVOCACY ADVANCEMENT

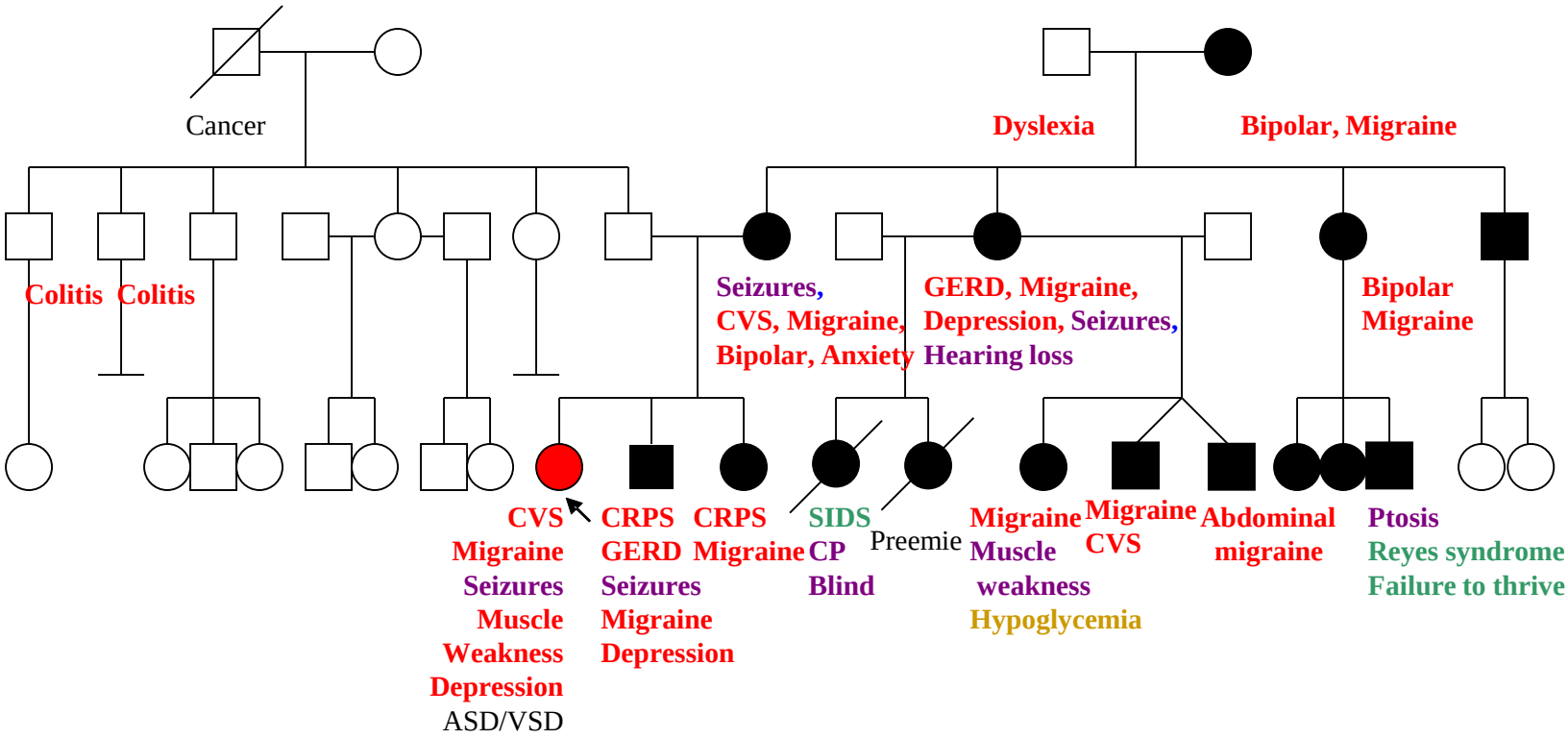
Thomas, age 22 years
POTS

- Presented as the lesser-affected brother of a girl with multi-system presumed “mitochondrial disease”.
- Had mild “functional” symptoms only in first decade, such as occasional pain, fatigue and dyautonomia.
- Episode of complex regional pain syndrome following removal of benign tumor on back.
- In early adolescence, developed episodes of POTS/pre-syncope that were dramatic, occurred with little warning, often in school.
- Episodes appeared like grand-mal seizures, paramedics called to school often.
- Episodes became frequent, sometimes followed by severe dysautonomia failure that required ICU admissions for up to a few weeks.
- Effectively disabled by his condition.

DYSAUTONOMIA INTERNATIONAL

AWARENESS ADVOCACY ADVANCEMENT

Maternal Inheritance of Functional Disorders - 1



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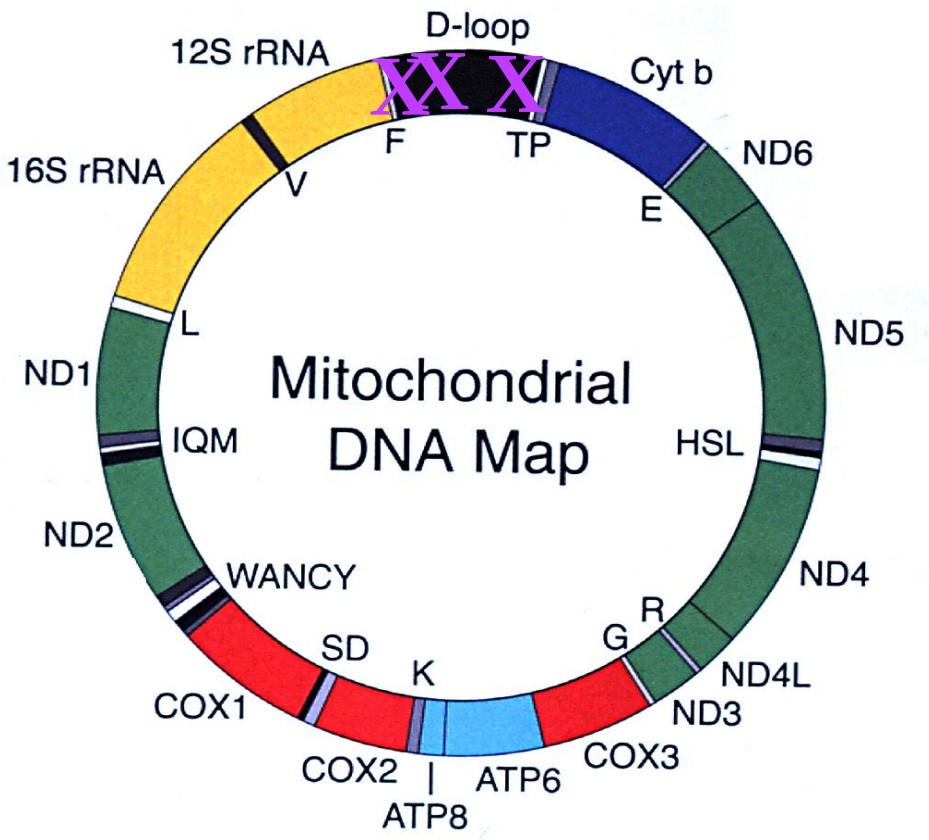
AWARENESS ADVOCACY ADVANCEMENT

Thomas' mtDNA



Three different length heteroplasmic variants

mtDNA control region – area involved in replication and transcription of mtDNA

DYSAUTONOMIA INTERNATIONAL

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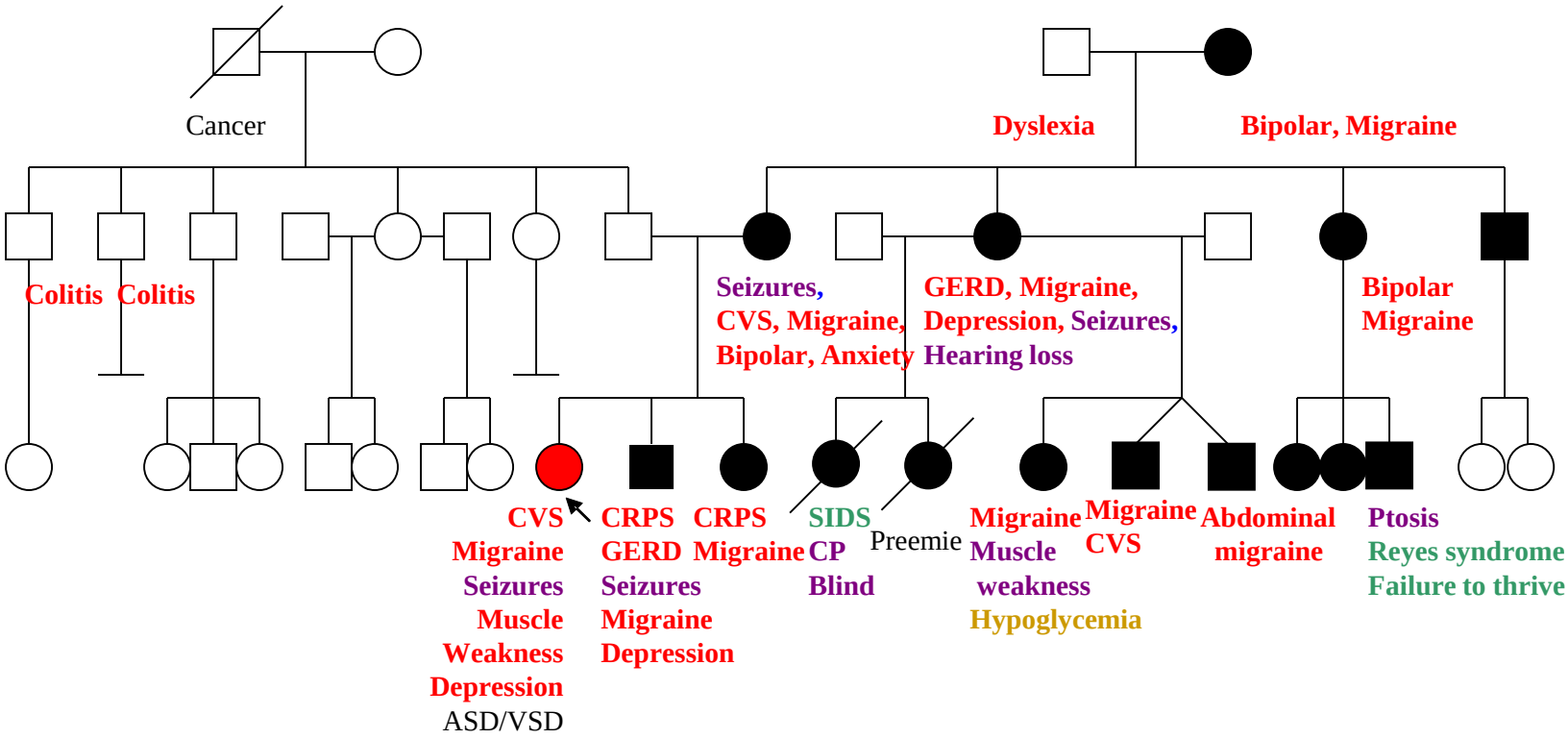

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- Episodes appeared like grand-mal seizures, paramedics called to school often.
- Episodes became frequent, sometimes followed by severe dysautonomia failure that required ICU admissions for up to a few weeks.
- Effectively disabled by his condition.
- Asked me for medical clearance to go SCUBA diving with his high-school class from a remote base on Catalina Island.

Thomas, age 22 years
POTS

- Placed on L-arginine supplementation, which dramatically improved his POTS to about one episode a year.
- L-arginine is an amino acid, part of natural protein. It is involved with nitric oxide synthesis, which dilates blood vessels. It is very effective in preventing stroke in MELAS.
- He DID go SCUBA diving with his class!
- On sequencing of nuclear-encoded mitochondrial proteins he was found to have a mutation in the *TRAP1* gene, p.Tyr229*
- His affected sisters and affected mother have the same mutation.
- Doing very well at present, essentially normal other than chronic fatigue (sleeps 10-11 hours at night) and some pain.

When to Suspect Mitochondrial Disease?

Suspect mitochondrial/metabolic disease if there are two or more of the following "**Red Flags**":

- Autistic spectrum disorder/pervasive developmental disorder
- Loss of milestones/regression
- Movement disorder (including ataxia, dystonia, chorea, tics)
- Stroke or stroke-like episodes
- Myopathy, especially ocular or cardiac
- Chronic bowel dysmotility (especially if severe or at more than one level)
- Cyclic vomiting
- Dysautonomia (including POTS, frequent tachycardia, unexplained fevers)
- Chronic pain condition (including migraine, myalgia)
- Chronic fatigue
- Mood disorders
- Waxing and waning clinical course (including altered mental status or psychosis)
- Hypoglycemia
- Metabolic acidosis (either renal tubular loss and/or anion gap)
- Elevated liver transaminases (including only trace elevated, if frequent)