

# MITOCHONDRIAL DISEASE AND AUTISM

*BRIDGING THE GAP*

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Biochemical Genetics, Pediatrics

Metabolic, Mitochondrial & Inherited Disorders

# OBJECTIVES

To provide basic background information on Mitochondrial Disease, its clinical features, diagnosis, treatment, prognosis, inheritance and to discuss its association with Autistic Spectrum Disorders (ASD).

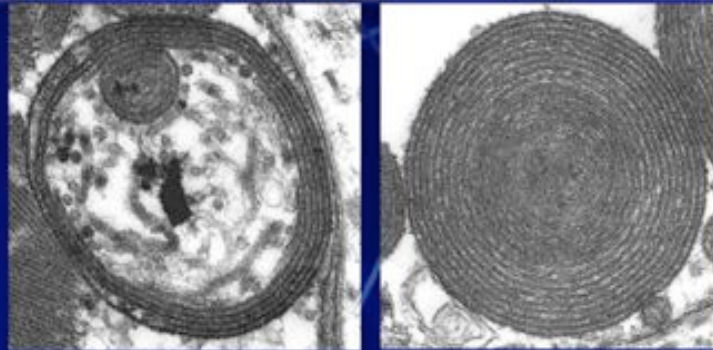
## DISCLAIMER

Dr Kendall and Virtual Medical Practice have no financial interest in any laboratory.

# THE BIG QUESTIONS

What are Mitochondria?

What is Mitochondrial Disease?

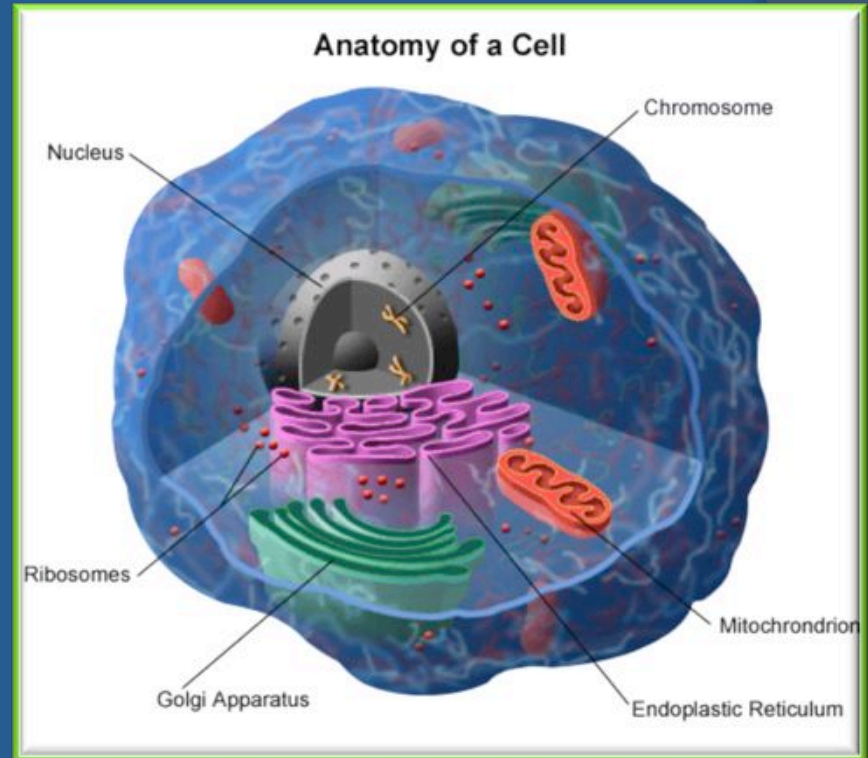


•Unusual mitochondria in child with mitochondrial disease

•Note many cristae on the right as if this organelle is trying to compensate for its lack of function.

# OUR BODIES CELLS

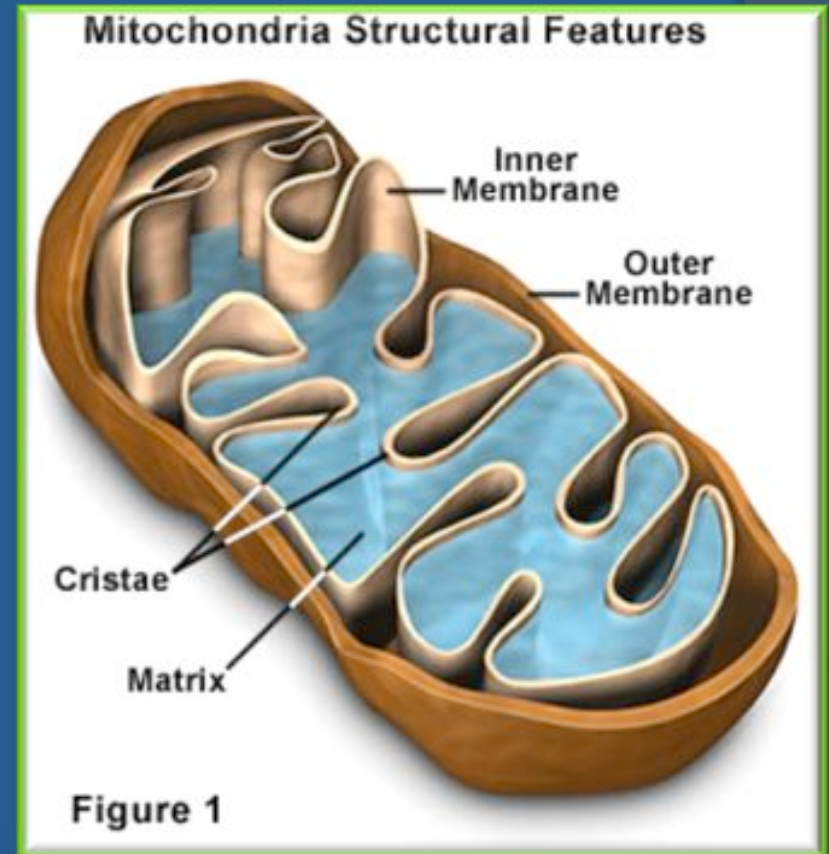
- Smallest functioning unit of our bodies
- Many cells together make up tissues
- Many sheets of tissues make up our organs





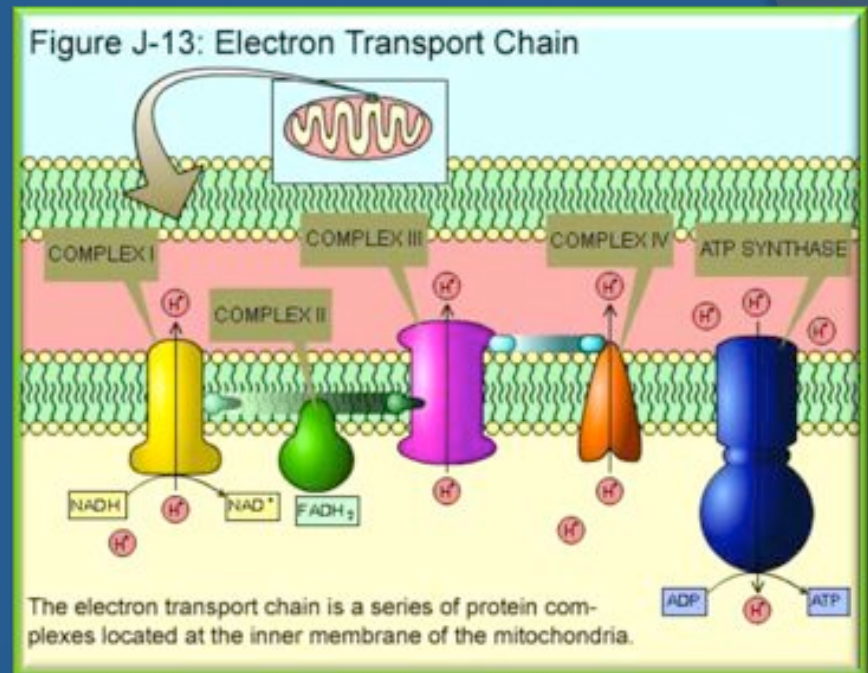
# THE POWERPLANTS

- Located inside our body cells
- Composed of an inner and outer membrane
- The energy producing pathway is the respiratory chain
- The respiratory chain consists of 5 complexes (groups of chemicals) that produce ATP



# THE RESPIRATORY CHAIN

- Oxygen & phosphate used to make energy
- Composed of five complexes or groups of chemicals with a total of ~90 subunits
- Energy packets are known as ATP



# ELECTRON TRANSPORT CHAIN



# MITOCHONDRIAL ENERGY DISORDERS

- Found in 1 in 4,000 individuals
- Carrier rate of common mtDNA mutations may be as high as 1 in 200
- Caused by an alteration in our inherited blueprint (gene mutation) or “toxic” affect of external factor such as medication
- Results in decreased energy production and localized or widespread problems



# THE GENETICS OF MITO DISEASE

- There are hundreds of genes involved in coding for the various proteins and other compounds involved in OXIDATIVE PHOSPHORYLATION or mitochondrial energy production
- These genes are contributed by two sets of inherited genetic material; the nuclear genes located inside the nucleus of our body cells and mitochondrial genes found inside the mitochondria of our cells
- **Nuclear genes** are inherited from both parents and contribute the vast majority of the information needed for energy production
- **Mitochondrial genes** are inherited EXCLUSIVELY through mom and contribute the remaining information



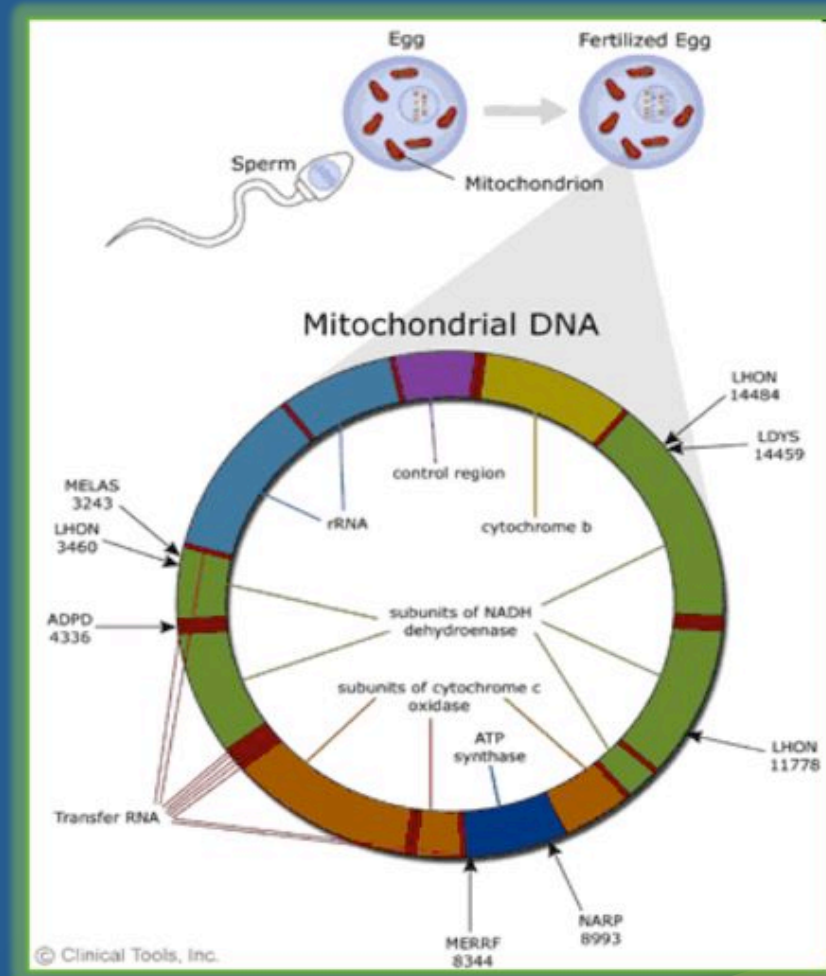
# FEATURES OF MITOCHONDRIAL NUCLEAR GENES

- Approximately 850 proteins are encoded for by the nuclear mitochondrial genes
- Many of these proteins are responsible for the control of electron transport chain structure and function and assembly
- Autosomal recessive inheritance of nuclear gene defects is probably the most common etiology of pediatric patients with mitochondrial disorders.

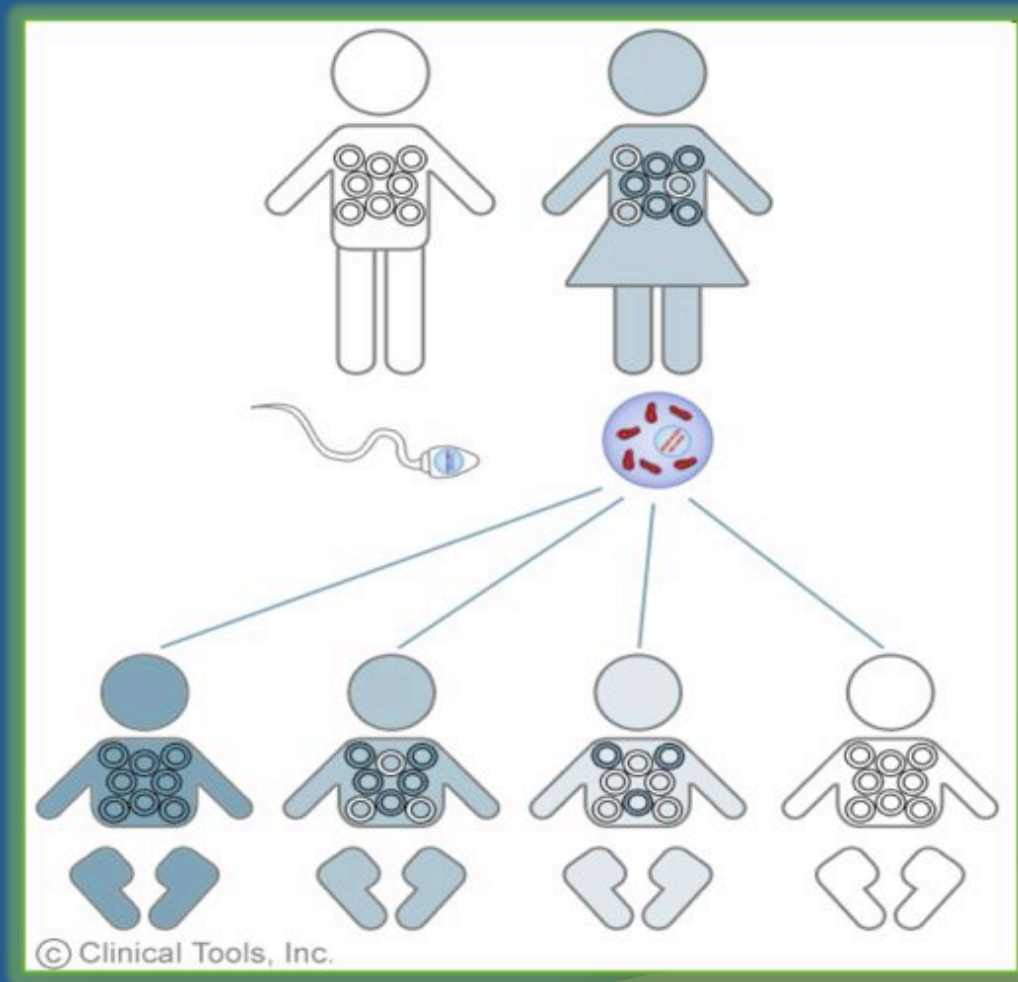
# FEATURES OF MITOCHONDRIAL DNA (MTDNA)

- Inherited exclusively through the maternal line
- Circular molecule, a number of copies in each mitochondrion (5-10 copies typical)
- 16,569 bases or pieces and 37 genes
- Mutated mtDNA may be present in varying amounts with wild type DNA (heteroplasmy)

# MITOCHONDRIAL DNA



# HETEROPLASMY OF MTDNA



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# SYMPTOMS I — *listed on [www.virtualmdpractice.com](http://www.virtualmdpractice.com)*

## ➤ BRAIN

- Developmental Delays
- Migraines
- Seizures
- Dementia
- Autistic Features
- Atypical Cerebral Palsy
- Neuro-psychiatric Disturbances
- Mental Retardation
- Strokes



# SYMPTOMS II — *listed on [www.virtualmdpractice.com](http://www.virtualmdpractice.com)*

## ➤ NERVES

- Absent reflexes
- Fainting
- Neuropathic pain
- Weakness (may be intermittent)
- Dysautonomia - temperature instability & other dysautonomic problems

## ➤ PANCREAS & OTHER GLANDS

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

# SYMPTOMS III — *listed on [www.virtualmdpractice.com](http://www.virtualmdpractice.com)*

- MUSCLES
  - Weakness
  - Cramping
  - Hypotonia
  - Muscle pain
  
- GASTROINTESTINAL PROBLEMS
  - Pseudo-obstruction
  - Dysmotility
  - Irritable bowel syndrome
  - Gastroesophageal reflux
  - Diarrhea or constipation

# SYMPTOMS IV — *listed on [www.virtualmdpractice.com](http://www.virtualmdpractice.com)*

- KIDNEYS
  - Renal tubular acidosis or wasting
  
- HEART
  - Cardiomyopathy
  - Cardiac conduction defects (heart blocks)
  
- LIVER
  - Liver failure
  - Hypoglycemia (low blood sugar)

# SYMPTOMS V — *listed on [www.virtualmdpractice.com](http://www.virtualmdpractice.com)*

## ➤ EARS & EYES

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

## ➤ SYSTEMIC

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

# COMMON PROBLEMS IN MITOCHONDRIAL ENERGY DISORDERS

- Central Nervous system (Brain) problems such as developmental delays including AUTISM AND AUTISTIC FEATURES, loss of function, seizures, hypotonia & weakness
- Failure to thrive
- Chronic fatigue
- Gastrointestinal issues such as chronic constipation
- Autonomic dysfunction such as irregular heart rate and blood pressure and temperature instability with heat intolerance.



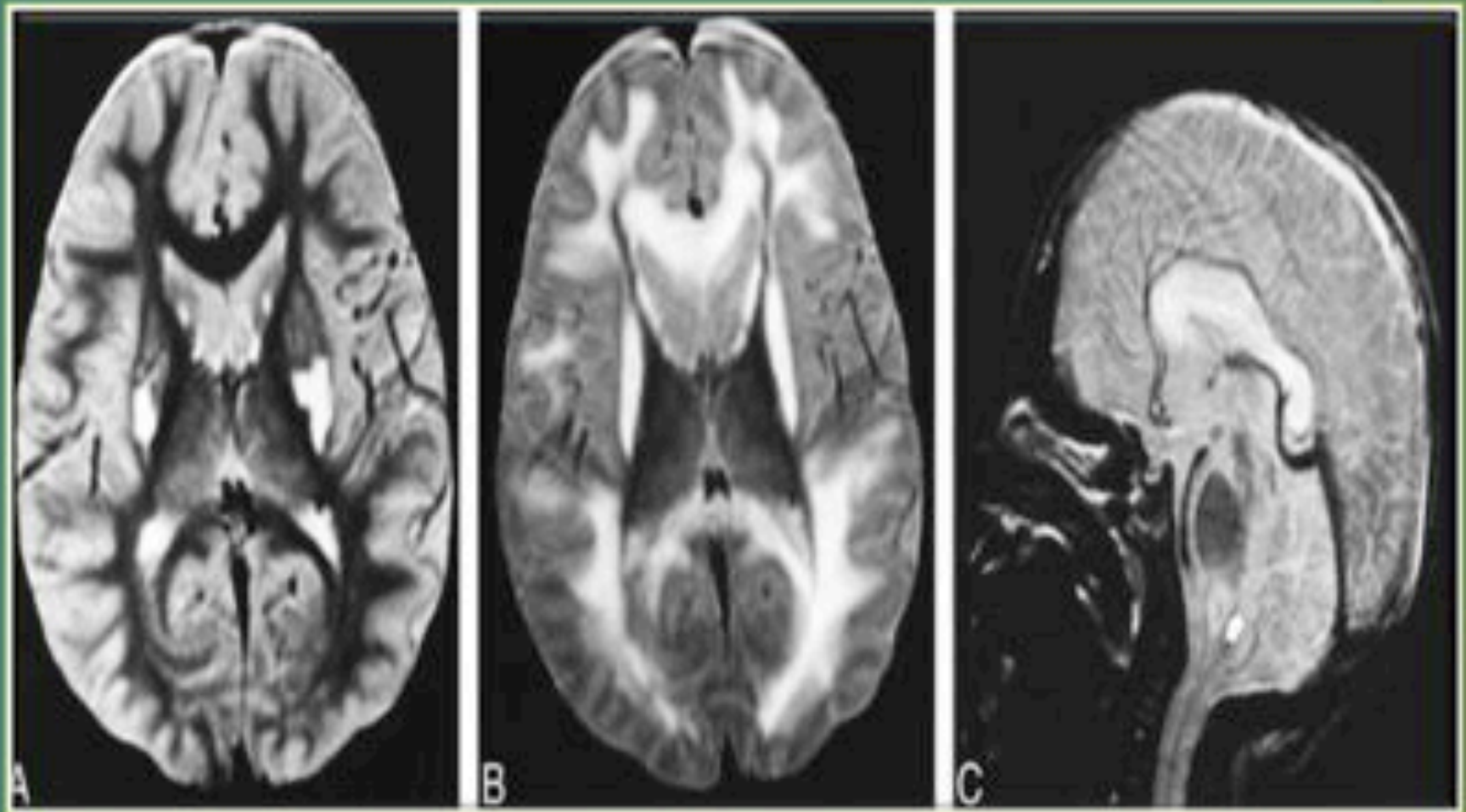
# CLINICAL FEATURES SUGGESTIVE OF MITOCHONDRIAL ENERGY DISORDERS

- Typical brain changes suggestive of Leigh disease or abnormalities in white matter
- Persistent, significant elevations in lactate (especially if in the brain) and other specific biochemical features
- Problems in many body systems suggestive of mitochondrial disease
- Strong family history of mitochondrial disease

# HOW IS MITOCHONDRIAL DISEASE DIAGNOSED? *TRADITIONAL EVALUATION*

- Clinical features, physical findings and minimal laboratory/radiographic studies, example specific brain lesions as seen in Leigh disease
- Clinical phenotype consistent with one of the well described subtypes of mitochondrial disease, such as MELAS and confirmed by gene test.
- Clinical features and findings suggestive of mitochondrial disease – tissue studies completed.

# LEIGH DISEASE MRI LESIONS

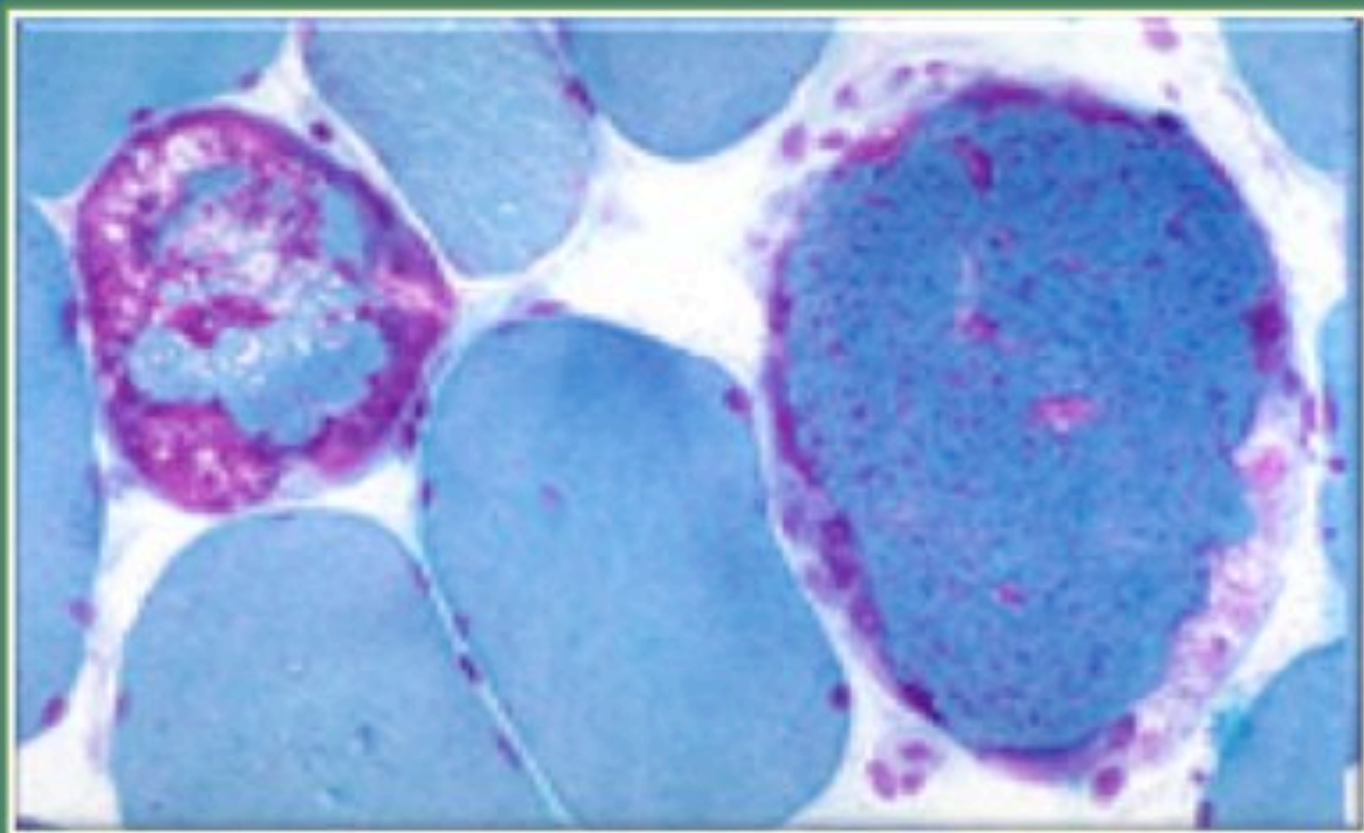


# DIAGNOSIS OF MITOCHONDRIAL ENERGY DISORDERS

- Abnormalities in mitochondrial structure/size/shape/number on tissue biopsy
- Enzymatic abnormalities on testing of the energy producing system (respiratory chain or electron transport chain)
- Specific DNA changes that cause mitochondrial disease



# RAGGED RED FIBERS





# EXAMPLES OF NUCLEAR GENE MITO DISEASE

- Complex I nuclear gene mutations - example NDUFV1 patients with leukodystrophy and myoclonic epilepsy
- Complex IV assembly gene mutations - example SURF1 mutations associated with Leigh disease

# EXAMPLES OF MTDNA DISEASE

- MELAS (Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke Like Episodes) due to tRNA 3243 mtDNA mutation
- MERRF (Myoclonic Epilepsy and Ragged Red Fibers) due to tRNA 8344 mutation

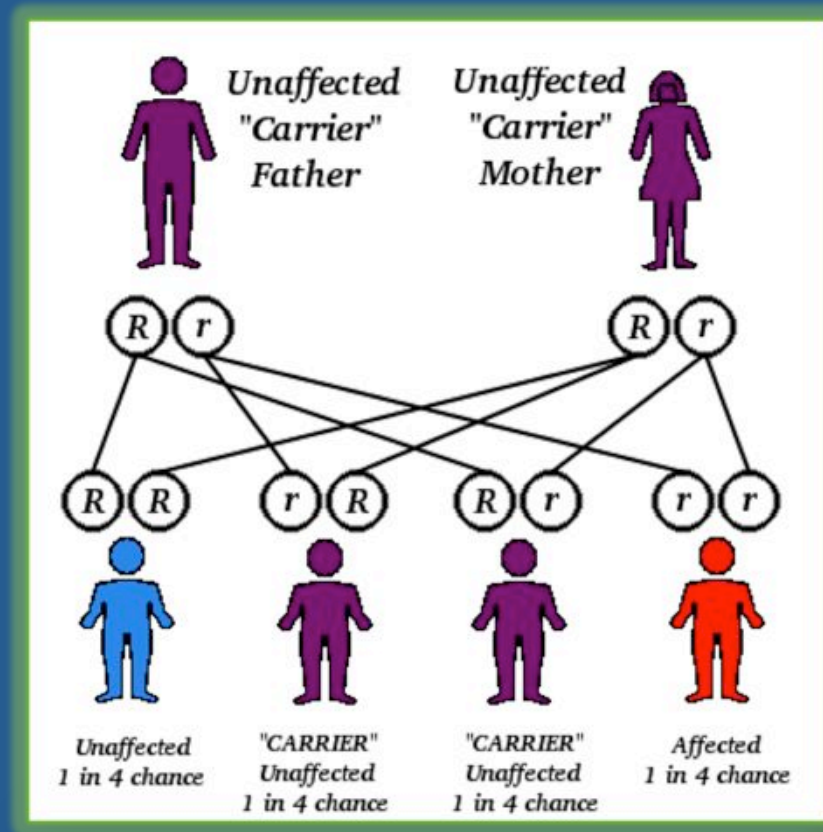
# PROGNOSIS OF MITOCHONDRIAL ENERGY DISORDERS

- Quite variable but typically progressive over time
- Patients can face severe disabilities and early death
- Many patients stabilize or show improvements with institution of care
- Problems typically worsen with stressors such as illness and surgery

# CURRENT TREATMENT OF MITOCHONDRIAL ENERGY DISORDERS

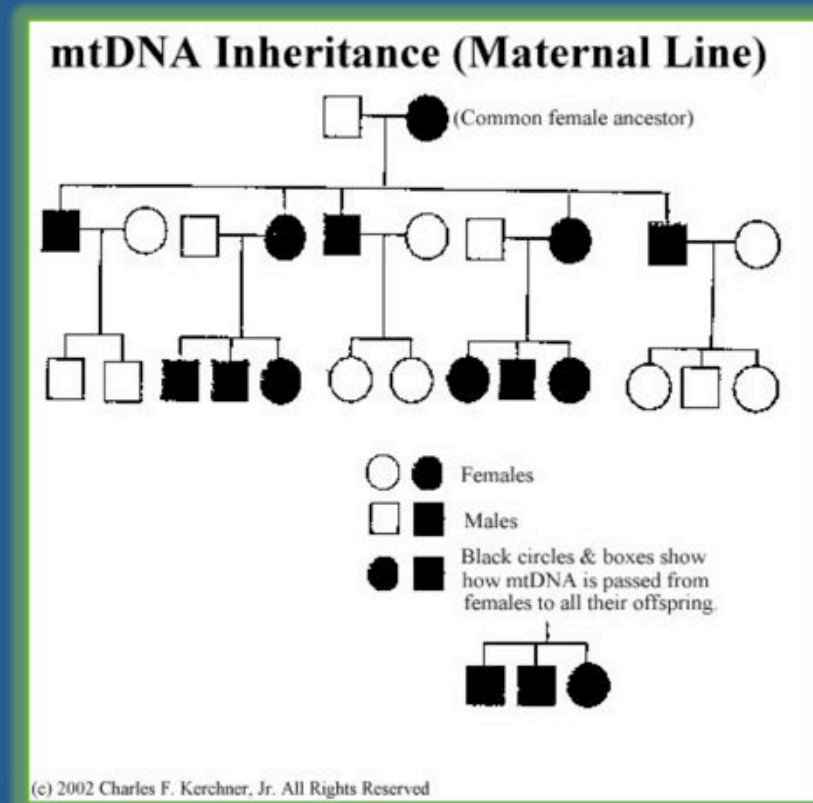
- Symptomatic – treat existing problems
- Preventative – early detection of associated problems
- Therapeutics very limited and include use of Coenzyme Q10

# INHERITANCE OF MITOCHONDRIAL ENERGY DISORDERS



*Autosomal Recessive Inheritance*

# INHERITANCE OF MITOCHONDRIAL ENERGY DISORDERS

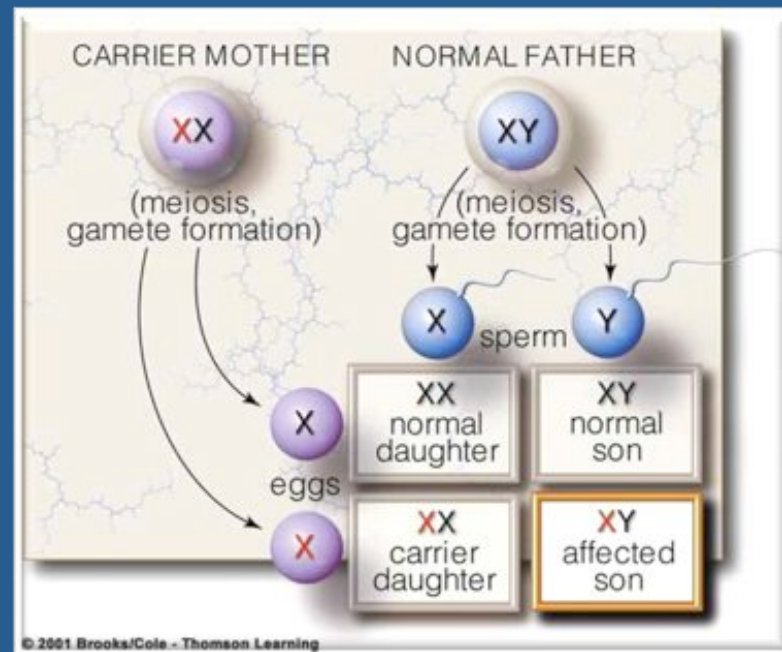


*Maternal Inheritance*



# INHERITANCE OF MITOCHONDRIAL ENERGY DISORDERS

- Autosomal Dominant forms
- Sporadic
- X-linked



# ADVANCEMENTS AND THE FUTURE

- Edison Pharma EPI 743 trial for Leigh Disease and MELAS patients
- Hemopoietic stem cell transplant for MNGIE
- Elimination of mtDNA mutation with nuclear transplant into healthy egg cells
- New less invasive testing including buccal swab enzyme testing and expanded gene panels to identify hundreds of the known mito genes

# HOT TOPIC IN MITOCHONDRIAL DISEASE...

Autism and Mito

# WHAT IS AUTISM?

- A complex neurobiological disorder that typically lasts throughout a person's lifetime, is a part of a group of disorders known as autism spectrum disorders (ASD) and affects the ability to communicate and relate to others
- Also associated with rigid routines and repetitive behaviors
- 1 in 90 individuals is diagnosed with autism making it more common than pediatric cancer, diabetes and AIDS combined
- Occurs in all racial, ethnic and social groups and is 4 times more likely to affect boys than girls.
- An underlying diagnosis is established in only 2% - 36% of cases

# MITO DISORDERS AND AUTISM

- One 2005 population based study in Portugal suggested that 7.2 out of 100 patients with ASD have an underlying mito disorder.
- A 2007 study by the same group revised their population figures and noted 4.1 out of 100 patients with autism had underlying mitochondrial disease.
- Although mito appears to be a rare cause of autism, it is one of the more common definable causes of ASD.

# CASE STUDY: ONE

One study evaluated five patients with ASD and family histories of mitochondrial DNA diseases.

- Three patients had isolated autistic features and two had additional neurological findings.
- Two patients had the common MELAS A3243G mutation.
- One patient had mtDNA depletion.



# CASE STUDY: TWO

Weissman et al reported the association of ASD with the mtDNA A4295G mutation in a 15 year old with a number of other neurological findings including hearing loss.

# UC DAVIS STUDY –

**GIULIVI ET.AL. JAMA, NOVEMBER 2010**

- Children with ASD are far more likely to have a defect in their ability to produce energy than typically developing children
- Discovered widespread reduced mitochondrial enzyme function among autistic children, affecting complex I in 60% of the patients
- Association established utilizing WBC (lymphocyte) testing

# ROSSIGNOL & FRYE – MOLECULAR PSYCHIATRY, JANUARY 2011

- Children on the autism spectrum also reside along a spectrum of mitochondrial dysfunction of varying severity
- Emphasized the need for ASD children to be screened for possible mitochondrial dysfunction citing improvements in children with ASD & mito dysfunction after initiation of mito disease management

# CONCLUSION OF STUDIES

- The link between mitochondrial dysfunction and autism is greater than suspected
- It remains uncertain if this association is due to a primary defect in mitochondrial functioning due to gene mutations or dysfunction caused by other factor(s).
- Mitochondrial disease should be considered when associated with other neurological and body system complications and/or a family history of mitochondrial disease.

# RECOMMENDED EVALUATION FOR ASD PATIENTS

➤ **TIER 1** – *basic work up recommended for all patients*

- CHROMOSOME MICROARRAY STUDIES
- COMPLETE METABOLIC PANEL, CBC, CPK
- AMMONIA LEVEL
- LACTATE AND PYRUVATE LEVELS
- CARNITINE, PLASMA TOTAL AND FREE
- COENZYME Q10 LEVEL
- PLASMA AND URINE AMINO ACIDS
- URINE ORGANIC ACIDS
- PLASMA ACYLCARNITINES
- THYROID FUNCTION TESTS

*list is located on our website, [www.virtualmdpractice.com](http://www.virtualmdpractice.com)*

# RECOMMENDED EVALUATION FOR ASD PATIENTS

- **TIER 2** – *depends on clinical features & results of Tier 1 testing*
  - MITOCHONDRIAL ENZYME AND/OR DNA TESTING
  - RETT SYNDROME DNA TESTING
  - PTEN MUTATIONAL ANALYSIS
  - NLGN3, NLGN4X, SHANK3, SNRPN GENE TESTING
  - LYSOSOMAL ENZYME TESTING
  - PEROXISOME DISEASE TESTING (VLCFAS)
  - CSF STUDIES FOR LACTATE AND PYRUVATE, AMINO ACIDS AND NEUROTRANSMITTERS
  - BRAIN MRI

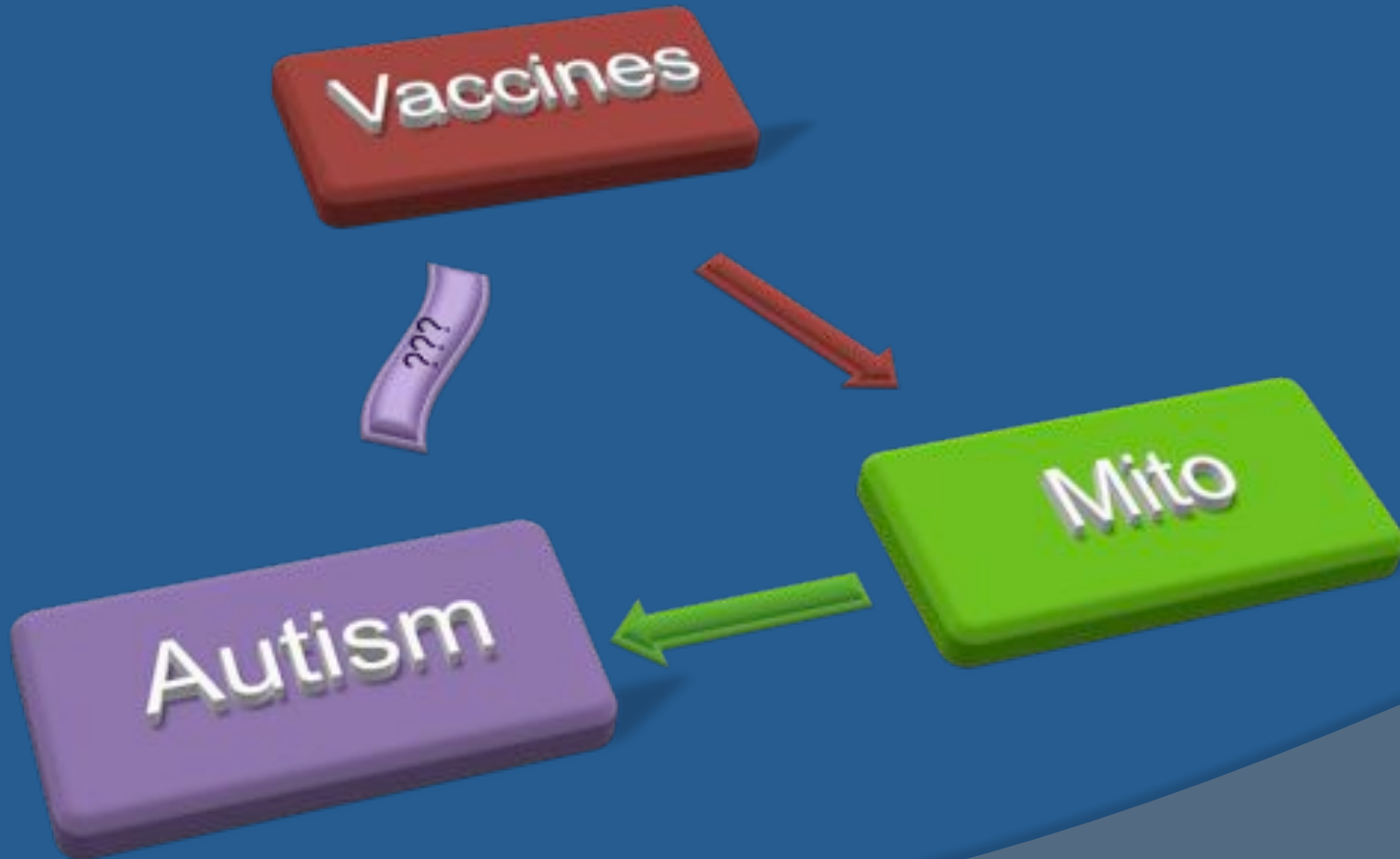
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# WHY IS IT IMPORTANT TO KNOW IF AN ASD PATIENT HAS MITO?

- For implementation of treatment & protocols
- Monitoring in affected individuals
- To determine recurrence risks for future children
- To determine risk for other family members

# MITO, AUTISM, AND VACCINES



# THANK YOU!

and

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