Clinical Overview and Diagnosis of Pediatric Mitochondrial Diseases

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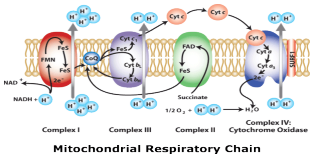
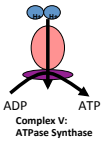
Definition of a Mitochondrial Disease

- Disorders of enzymes or enzyme complexes directly involved in the generation of chemical energy by **oxidative phosphorylation**
- Primary *vs.* Secondary



Mitochondrial Respiratory Chain

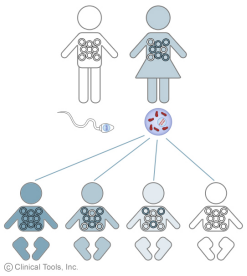


http://public2.bcm.tmc.edu/pediatrics/index.cfm?Realm=9999426&This_Template=respiratory_chain

More Common than We Think

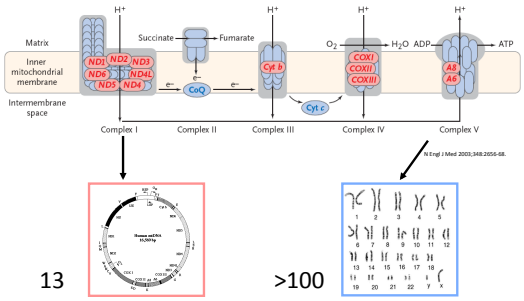
- Primary mitochondrial disease may be one of the most commonly encountered classes of genetic diseases
  - "Any symptom at any age"
    - Can occur at any age
    - Can involve almost any organ system
  - Incidence may be 1:7,000, or even higher

1.Maternal Inheritance



http://images.clinicaltools.com/images/gene/heteroplasmy_diagram_large.jpg

2. Various Causes of Mitochondrial Diseases

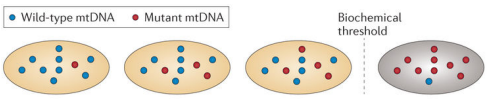


13 >100

Any mode of inheritance is possible

- Sporadic
  - (mtDNA has a high mutation rate, including nucleotide substitutions and deletions/insertions)
- X-linked
- Autosomal recessive
- Autosomal dominant
- Maternal/mt inheritance

3. Heteroplasmy and 4. Threshold Effect

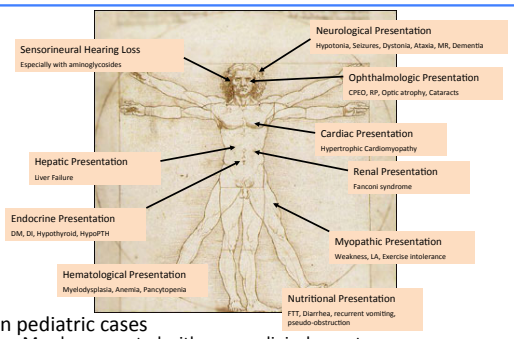


Nature Reviews | Genetics

Nature Reviews Genetics **16**, 530–542 (2015)

- Each mitochondrion contains 2 to 10 copies of mtDNA
- Each cell may harbor hundreds to thousands of mitochondria
- Mitochondrial populations may differ among tissues
- It takes a "threshold" number of affected mitochondria to manifest as disease

Clinical Presentations



In pediatric cases

May be presented with severe clinical symptoms

Life threatening acidosis, cardiopulmonary compromise

Structural defects

Current Diagnostic Methods

- Clinical suspicion
- Biochemical analysis
  - Lactate, pyruvate
  - amino acid analysis, acylcarnitine profile, urine organic acid test
- Mitochondrial specific test
  - Biopsy for muscle cells, skin fibroblasts
  - Enzyme assays for respiratory chain complexes
  - Oxygen consumption rate
- Genetic tests
  - Sanger sequencing
  - Next generation sequencing (NGS)
    - Panel test, whole exome sequencing

Complexity of Mitochondrial Diseases

- Hard to rule-out even after genetic testing!
- Blood draws and biopsies are not always definitive!
  - Sampling of a less affected, or unaffected region of the body or tissue may not yield a characteristic defect
- Genetic counseling is very difficult
  - Without confirmatory genetic testing, any inheritance pattern is possible.
  - "Your chances of having another child affected with mitochondrial disease is anywhere from 0% to 100%".

Case #1

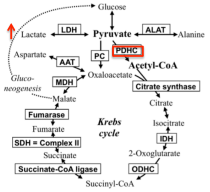
- 1 day old male
- Born at full term without complications
- Previous male child died at 6 months with lactic acidosis
- After delivery
  - Lethargy and poor feeding
  - Severe lactic acidosis
  - Transferred to Mount Sinai NICU
  - Lactate: unmeasurable >15 with high pyruvic acid
  - Hypoglycemia due to maternal diabetes
  - Head ultrasound: absence of corpus callosum
  - Cardiac echo: VSD

Case#1 Follow Up

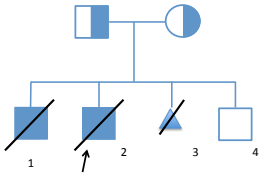
- Mitochondrial disorder suspected
  - Particularly pyruvate dehydrogenase deficiency (PDHD)
  - X-linked inherited common with *PDHA1* mutations
- Developmentally delayed
- Visual impairment
- Became more hypertonic and spastic in lower extremities
- Poor feeding requiring NG tube
- Carb restricted diet, bicitra, thiamin
- Lactate consistently elevated with acidosis
- Died from RSV virus bronchiolitis at 3 yo

Case#1 Genetic Tests

- PDH & Complex V NGS panel tests
  - *PDHA1*:
    - no significant variant detected
  - *PDHB*: homozygous for a novel variant
- Diagnosis: PDH deficiency



Case#1 Counseling



1 in 64 chance to have 3 affected pregnancies
#4 baby is now 1 week old

Case #2

- 2 days old male
- Born at 37 wks GA via C-section due to NRFHT.
- Pregnancy complicated by IUGR
- Required PPV briefly at birth, Apgars 7 and 8.
- After delivery
  - 2 hours: temperature instability, transferred to NICU
  - Within 12 hours: tachypnea, not-well appearing
  - Severe metabolic acidosis
    - ABG: pH 7.25, PCO2 17, PO2 79, HCO3 8, BE -15.2
  - Lactate: unmeasurable >15
  - Pulmonary hypertension
  - Normal brain structure

Case#2 Follow Up

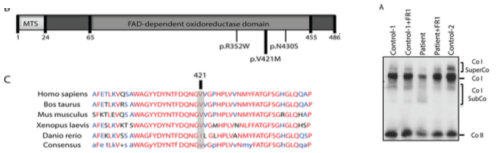
- Mitochondrial disorder suspected
- Developmentally delayed
- Became more hypertonic and spastic in lower extremities
- Poor feeding requiring NG tube
- Bicitra, thiamin, riboflavin, levocarnitine
- Lactate consistently elevated with acidosis
- Lactic acidosis refractory to medical management
- Died from rhinovirus bronchiolitis during infancy

Case#2 Genetic Tests

- PDH deficiency tests
  - PDHA1: no significant variant detected
  - PDHB: no significant variant detected
- GeneDx Combined Mito Genome + Mito Nuclear Gene Panel
  - FOXRED1
    - Compound heterozygous variants

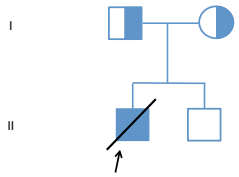
FOXRED1

- FAD-dependent oxidoreductase-containing domain 1
- Required for assembly of complex I
- Mutations in FOXRED1 cause Leigh syndrome, lactic acidosis, epilepsy, psychomotor retardation
- 6 variants have been previously reported



Mol Cell Biol. 2016 Jul 29;36(16):2132-40

Case#2 Counseling



Case #3

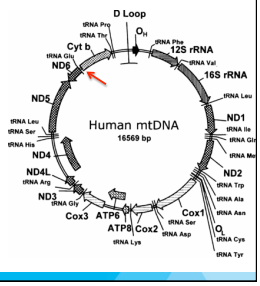
- 2 weeks old male
- Born at full term with prenatal complication of ventriculomegaly
- After delivery
  - Sleepiness and poor feeding with hypotonia
  - Lethargy and hypothermia at 2 weeks
  - NBS positive for glutaric aciduria
  - Lactic acidosis
  - Transferred to Mount Sinai NICU
  - Lactate: unmeasurable >15

Case#3 Follow Up

- Mitochondrial disorder suspected
- Developed seizures
- Normal brain structure
- Cardiac echo: pulmonary hypertension
- Ventilator dependent with respiratory instability
- Lactate consistently elevated
- Glutaric aciduria ruled out
- Died during early infancy

Case#3 Genetic Tests

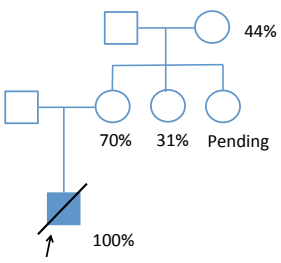
- GeneDx Combined Mito Genome + Mito Nuclear Gene Panel
  - MT-TE gene
  - m.14709T>C
  - Homoplasmy



Case#3 Counseling

MT-TE m.14709T>C variant

- Associated with diabetes and deafness
- Congenital myopathy, mental retardation, cerebellar ataxia may occur
- Homoplasmy and high percentages of heteroplasmy (80 to 90%) suggested clinically significant
- Symptoms vary
- A previous case with severe infantile lactic acidosis



Conclusions

- Wide variety of tests became available
  - Better diagnosis
  - Very useful for counseling (risk assessment, prenatal diagnosis)
  - But still many cases without diagnosis
- Identifying genetic causes is very helpful for families
- Effective therapy not available
- Genetic counseling is extremely important
  - Genetic counselors, Geneticists
  - Prenatal testing, PGD options are discussed
  - But not on further techniques based on current standard of care