MITOCHONDRIAL DISEASE PRIMER

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Disclosures & Disclaimers

• UMDF fellow, SMAB member.
• North American Mitochondrial Disease Consortium site PI.
• Advisory Board of the Mitochondrial Medicine Society and MitoAction.
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• Consulting for Sanofi Genzyme, Stealth Biotherapeutics, Alexion, Lumleian, Homology, MitoBridge, Akros, Astellas.
Cases

- 8 mo female with jaundice and liver failure
- 3 yo male with developmental regression and seizures
- 15 yo female with migraines, severe constipation, fainting
- 24 yo male with speech and balance problems
- 30 yo female with enlarged heart and strokes
- 55 yo male with weakness, muscle pain, hearing loss
- 71 yo female with dementia, diabetes, jerking limbs
Outline:

• Overview of the mitochondria
• Overview of mitochondrial function
• Overview of mitochondrial genetics
• Overview of mitochondrial disease
Overview: The mitochondria
Overview: the mitochondria

1 to 1000s/cell

Overview: the mitochondria

What does mitochondria do?
Overview: the mitochondrial function
Overview: the mitochondrial function

http://www.bio.davidson.edu/
Overview: the mitochondrial function

The electron transport chain

Nat Rev Genet. 2012 December; 13(12): 878–890
Overview: the mitochondrial function
Overview: The mitochondria

Christian A. Wurm et al. PNAS 2011;108:13546-13551
Overview: The mitochondria

Vafai et al. Nature 2013:491, 374–383
Overview: the mitochondrial function

Vafai et al. Nature 2013:491, 374–383

https://www.bbe.caltech.edu
Overview: the mitochondrial function
Overview: the mitochondria

The unique genetics
Overview: the mitochondria

The Mitochondrial Organelle Bi-genomic Input

mtDNA

nDNA
Overview: the mitochondria
The electron transport chain

<table>
<thead>
<tr>
<th>Polypeptides</th>
<th>Complex I</th>
<th>Complex II</th>
<th>Complex III</th>
<th>Complex IV</th>
<th>Complex V</th>
</tr>
</thead>
<tbody>
<tr>
<td>mtDNA-encoded subunits</td>
<td>7</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>nDNA-encoded subunits</td>
<td>~39</td>
<td>4</td>
<td>10</td>
<td>10</td>
<td>~14</td>
</tr>
<tr>
<td>Assembly proteins</td>
<td>~11</td>
<td>~2</td>
<td>~9</td>
<td>~30</td>
<td>~3</td>
</tr>
</tbody>
</table>
Overview of nDNA
Polymerase Gamma (POLG)
<table>
<thead>
<tr>
<th>Condition</th>
<th>Gene(s)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpers–Huttenlocher syndrome (AHS)</td>
<td>nDNA (POLG-related)</td>
<td>Intractable epilepsy, psychomotor regression and liver disease; might also include the clinical features of MCHS and MEMSA</td>
</tr>
<tr>
<td>Childhood myocerebrohepatopathy spectrum (MCHS)</td>
<td></td>
<td>Neuropathy, ataxia, hypotonia, myoclonus (spontaneous muscle contractions), choreoathetosis (the occurrence of involuntary jerky, writhing movements of muscles or muscle groups) and Parkinsonism, in addition to renal tubulopathy</td>
</tr>
<tr>
<td>Ataxia neuropathy spectrum (ANS; previously referred to as mitochondrial recessive ataxia syndrome (MIRAS) and sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO))</td>
<td></td>
<td>Sensory axonal neuropathy with variable sensory and cerebellar ataxia</td>
</tr>
<tr>
<td>Myoclonic epilepsy myopathy sensory ataxia (MEMSA; previously referred to as spinocerebellar ataxia with epilepsy (SCAE))</td>
<td></td>
<td>Epilepsy, PEO, seizures, dysarthria, dementia, spasticity and myopathy</td>
</tr>
<tr>
<td>Chronic progressive external ophthalmoplegia (CPEO)</td>
<td>TYMP, which encodes thymidine phosphorylase</td>
<td>Gastrointestinal dysmotility, muscle weakness and atrophy, neuropathy, retinopathy, hearing loss, leukoencephalopathy and depleted TYMP activity</td>
</tr>
<tr>
<td></td>
<td>POLG1, which encodes α-DNA polymerase subunit γ1</td>
<td>Ataxia, peripheral sensory neuronopathy, Parkinsonism, premature ovarian failure, psychiatric symptoms, MELAS syndrome and epilepsy</td>
</tr>
<tr>
<td></td>
<td>POLG2, which encodes DNA polymerase subunit γ2</td>
<td>Ptosis and proximal myopathy, dystrophy, cerebellar ataxia and gastrointestinal symptoms</td>
</tr>
<tr>
<td>Mitochondrial neurogastrointestinal encephalopathy (MNGIE) syndrome</td>
<td>TYMP, RRM2B and POLG</td>
<td>Gastrointestinal dysmotility, muscle weakness and atrophy, PEO, neuropathy, retinopathy, hearing loss, leukoencephalopathy* and depleted TYMP activity</td>
</tr>
</tbody>
</table>

Gorman et al. Nature reviews primers 2016
Overview of nDNA

MENDELIAN GENETICS AND HUMANS

Inheritance Patterns

**Autosomal recessive:**
Involves a recessive allele on a non-sex chromosome

**Autosomal dominant:**
Involves a dominant allele on a non-sex chromosome

**X-linked recessive:**
Involves a recessive allele on the X-chromosome

**X-linked dominant:**
Involves a dominant allele on the X-chromosome

**Y-linked:** Involves an allele on the Y-chromosome

**Sporadic/De novo**
Overview of mtDNA

- 16,569 bp
- Encodes 37 proteins:
  - 22 tRNAs
  - 13 respiratory chain peptides
  - 2 ribosomal
- 10s copies/mitochondrion, 100–1000s/cell
- Limited DNA repair (↑mutation rate)
Overview of mtDNA

• Maternal inheritance
Point mutations

Deletions/Duplications
Overview of mtDNA

- **MELAS**: Mitochondrial Encephalomyopathy, Lactic Acidosis and Strokes
- **MERRF**: Myoclonic Epilepsy with Ragged Red Fibers
- **LHON**: Leber’s Hereditary Optic Neuropathy
- **NARP**: Neuropathy, ataxia and retinitis pigmentosa
- **KSS/PEO**: Kearns Sayre syndrome/Progressive external ophthalmoplegia.
<table>
<thead>
<tr>
<th></th>
<th>KSS</th>
<th>MERRF</th>
<th>MELAS</th>
<th>NARP/ MILS</th>
<th>LHON</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SEIZURES</strong></td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>ATAXIA</strong></td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>STROKE</strong></td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>MYOCLONUS</strong></td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>NEUROPATHY</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>PEO</strong></td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>OPTIC NEUROPATHY</strong></td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>RETINOPATHY</strong></td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>HEART BLOCK</strong></td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>WPW</strong></td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Overview of mtDNA

- 1:200 people have an mtDNA mutation*
- Random segregation
- Threshold expression
- Heteroplasmy

* Chinnery et al 2008
Overview of mtDNA

- Mutant mitochondrion
- Normal mitochondrion
- Nucleus

Oocyte maturation and mtDNA amplification

Fertilization

- High level of mutation (affected offspring)
- Intermediate level of mutation (mildly affected offspring)
- Low level of mutation (unaffected offspring)

Primordial germ cell containing mutant mtDNA

Primary oocytes

Mature oocytes

http://clinicalgate.com/the-human-microbiome/
Overview of mtDNA

Respiratory chain dysfunction
• Primary Mitochondrial Disease
Vs.
• Secondary Mitochondrial Dysfunction
Overview of mitochondrial disease

Mitochondrial damage and somatic mtDNA mutations

Progressive bioenergetic decline

Degenerative disease
- Neurological
- Muscular
- Cardiac
- Renal
- Gastrointestinal

Metabolic disease
- Diabetes and obesity
- Thermoregulation
- Stress and trauma

Aging
- Apoptosis
- Senescence

Cancer
- Initiation
- Promotion
- Metastasis

Immunological disease
- Infection
- Inflammation
- Fever
- Autoimmunity

OXPHOS dysfunction
- Decreased energy, increased ROS
- Altered REDOX regulation of gene expression and metabolism
- Altered calcium homeostasis

mtDNA variation
- Ancient adaptive polymorphisms
- Recent deleterious mutations

nDNA variation
- Deleterious mutations
- Polymorphisms
- Epigenomic changes

Environmental factors
- Energy resources
- Energy demands
- Toxins
Overview of mitochondrial disease
Where does Mitochondrial Disease Hide?

- Diabetes Clinics
- Cancer Hematology Clinics
- Epilepsy Clinics
- Psychiatric Facilities
- Sudden Infant Death Syndrome SIDS
- GI Dysmotility Clinics
- Rheumatology/Multiple Sclerosis Clinics
- Unexplained Liver Failure
- Unexplained Heart Failure
- Unexplained Kidney Disease
- Unexplained Blindness

Overview of mitochondrial disease

- Lates accepted prevalence is 1 in 4,300*

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Prevalence per 100,000 individuals (95% CI)</th>
<th>Region</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6</td>
<td>8.9 (5.3–14)</td>
<td>Western Sweden</td>
<td>189</td>
</tr>
<tr>
<td>0–10</td>
<td>15 (9.8–21)</td>
<td>Central region of Portugal</td>
<td>190</td>
</tr>
<tr>
<td>0–16</td>
<td>4.7 (2.8–7.6)</td>
<td>Western Sweden</td>
<td>189</td>
</tr>
<tr>
<td>0–16</td>
<td>6.2 (4.5–8.4)*</td>
<td>South eastern Australia</td>
<td>9</td>
</tr>
<tr>
<td>0–16</td>
<td>71 (32–136)*</td>
<td>South eastern Australia (families of Lebanese ancestry)</td>
<td>9</td>
</tr>
<tr>
<td>0–18</td>
<td>7.5 (5–10)</td>
<td>North West Spain</td>
<td>191</td>
</tr>
<tr>
<td>0–18</td>
<td>~12</td>
<td>Northern Finland</td>
<td>192</td>
</tr>
<tr>
<td>Childhood</td>
<td>~11</td>
<td>Ireland</td>
<td>10</td>
</tr>
<tr>
<td>Childhood</td>
<td>~10</td>
<td>Japan</td>
<td>193</td>
</tr>
<tr>
<td>Adults (&gt;16)</td>
<td>9.6 (8.3–11)</td>
<td>North East of England (mtDNA)</td>
<td>11</td>
</tr>
<tr>
<td>Adults (&gt;16)</td>
<td>2.9 (2.2–3.7)</td>
<td>North East of England (nDNA)</td>
<td>11</td>
</tr>
</tbody>
</table>

Gorman et al. Nature reviews primers 2016

Overview of mitochondrial disease

• Any age – infancy to adulthood
• Multi-organ dysfunction
• Variable severity
• Progressive
Overview of mitochondrial disease

An extraordinary clinical spectrum of mitochondrial diseases:

- underdiagnosed "What is this complex disorder?"
- over diagnosed "This disorder is so complex that is must be mitochondrial!".
Overview of mitochondrial disease

• When should I suspect mitochondrial disease

‘...any organ, any symptom, any age’
Overview of mitochondrial disease

• Red flag symptoms
Neurologic
1. Cerebral stroke-like lesions in a nonvascular pattern
2. Basal ganglia disease
3. Encephalopathy, recurrent or with receiving valproate
4. Neurodegeneration
5. Epilepsia Partialis Continua
6. Myoclonus
7. Ataxia
8. MRI findings consistent with Leigh disease
9. Characteristic MRS peaks
   a. Lactate peak at 1.3 ppm TE at 35 and 135
   b. Succinate peak at 2.4 ppm

Ophthalmologic
1. Retinal degeneration
2. Ophthalmoplegia/paresis
3. Fluctuating, dysconjugate eye movements
4. Ptosis
5. Sudden- or insidious-onset optic neuropathy/atrophy

Gastroenterologic
1. Unexplained or valproate induced liver failure
2. Severe dysmotility
3. Pseudo-obstructive episodes

Cardiovascular
1. Hypertrophic cardiomyopathy with rhythm disturbance
2. Unexplained heart block in a child
3. Cardiomyopathy with lactic acidosis (> 5 mM)
4. Dilated cardiomyopathy with muscle weakness
5. Wolff-Parkinson-White arrhythmia

Other
1. Exercise intolerance out-of-proportion to weakness
2. Delayed waking from general anesthesia
3. Episodes of acute rhabdomyolysis
4. Unexplained hypotonia, failure-to-thrive, and acidosis

http://www.mitosoc.org/toolkit/
Overview of mitochondrial disease

http://www.stlukeseye.com/conditions/RetinitisPigmentosa.html
Overview of mitochondrial disease

Myopathy
Encephalopathy
Exercise intolerance
Ophthalmoplegia
Peripheral neuropathy
Ataxia
Deafness
MERRF/MELAS
Myocardiopathy
Diabetes
Retinopathy
Liver disease
Kidney disease
Intestinal disease
Optic atrophy
Leigh syndrome
Dysmorphia
Bone marrow dysfunction
Alpers syndrome

Adults (n = 390)

Children (n = 220)

SIMD/NAMA: Courtesy of Dr A Lombes Hopital La SalpêtrièreUniversité Paris VI
# Overview of mitochondrial disease

**Most common reasons for referral**

<table>
<thead>
<tr>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotonia</td>
<td>Fatigue +++</td>
</tr>
<tr>
<td>Seizures</td>
<td>Shortness of breath, air hunger</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>Muscle pain</td>
</tr>
<tr>
<td>Elevated lactate levels</td>
<td>GI dysmotility</td>
</tr>
<tr>
<td>Abnormal MRI images</td>
<td>Dysautonemia/POTS</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Multiple symptoms in many organ system that do not seem to be related</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td></td>
</tr>
<tr>
<td>GI dysmotility</td>
<td></td>
</tr>
</tbody>
</table>

**GI dysmotility**

**Fatigue +++**

**Shortness of breath, air hunger**

**Muscle pain**

**GI dysmotility**

**Dysautonemia/POTS**

**Multiple symptoms in many organ system that do not seem to be related**
Overview of mitochondrial disease

Metabolic Stress → Episodic Phenotype

Organ Failure

Observables Dysfunction

TIME

OBSERVABLE DYSFUNCTION

normal

mild

aging

severe

moderate
Diagnostic Evaluation: The problem

- Nonspecific symptoms
- There is no universally accepted diagnostic algorithm for mitochondrial disorders
- There is no gold standard diagnostic method.
- Enzyme (ETC) testing may produce false positive and false negative results.
- Molecular testing is positive in 25-45% of the cases at best.
Table Mitochondrial disease criteria (simplified version for bedside use)*

<table>
<thead>
<tr>
<th>I. Clinical signs and symptoms, 1 point/symptom (max. 4 points)</th>
<th>II. Metabolic/imaging studies (max. 4 points)</th>
<th>III. Morphology (max. 4 points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Muscular presentation (max. 2 points)</td>
<td>B. CNS presentation (max. 2 points)</td>
<td>C. Multisystem disease (max. 3 points)</td>
</tr>
<tr>
<td>Ophthalmoplegia†</td>
<td>Developmental delay</td>
<td>Hematology</td>
</tr>
<tr>
<td>Facies myopathica</td>
<td>Loss of skills</td>
<td>GI tract</td>
</tr>
<tr>
<td>Exercise intolerance</td>
<td>Stroke-like episode</td>
<td>Endocrine/growth</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>Migraine</td>
<td>Heart</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>Seizures</td>
<td>Kidney</td>
</tr>
<tr>
<td>Abnormal EMG</td>
<td>Myoclonus</td>
<td>Vision</td>
</tr>
<tr>
<td></td>
<td>Cortical blindness</td>
<td>Hearing</td>
</tr>
<tr>
<td></td>
<td>Pyramidal signs</td>
<td>Neuropathy</td>
</tr>
<tr>
<td></td>
<td>Extrapyramidal signs</td>
<td>Recurrent/familial</td>
</tr>
<tr>
<td></td>
<td>Brainstem involvement</td>
<td></td>
</tr>
</tbody>
</table>

* Score 1: mitochondrial disorder unlikely; score 2 to 4: possible mitochondrial disorder; score 5 to 7: probable mitochondrial disorder; score 8 to 12: definite mitochondrial disorder.
† This specific symptom scores 2 points.
‡ This symptom in a higher percentage scores 4 points.

GI = gastrointestinal; L/P = lactate/pyruvate; COX = cytochrome c oxidase; SDH = succinate dehydrogenase; EM = electron microscopy; EMG = electromyography; TA = tricarbon acid.
<table>
<thead>
<tr>
<th>Metabolic Screening (in all patients)</th>
<th>Metabolic Screening in spinal fluids (for patients with neurologic symptoms)</th>
<th>Characterize Systemic Involvement</th>
<th>Clinical Neurogenetic Evaluation (for those with developmental delays)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic Chemistries</td>
<td>Lactate &amp; Pyruvate</td>
<td>Echocardiogram</td>
<td>Karyotype</td>
</tr>
<tr>
<td>Liver enzymes &amp; Ammonia</td>
<td>Quantitative Amino Acids</td>
<td>Electrocardiogram</td>
<td>Fragile X testing</td>
</tr>
<tr>
<td>Complete Blood Count</td>
<td>Neurotransmitter studies</td>
<td>Ophthalmic exam</td>
<td>Neurology Consult</td>
</tr>
<tr>
<td>Creatine Kinase</td>
<td>Routine Studies including glucose, protein, &amp; cell count</td>
<td>Auditory exam</td>
<td>Genetics Consult</td>
</tr>
<tr>
<td>Blood Lactate, &amp; Pyruvate</td>
<td></td>
<td>Brain MRI</td>
<td></td>
</tr>
<tr>
<td>Quantitative Plasma Amino Acids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantitative Urine Organic Acids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma Acylcarnitine Profile</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Negative results have a high false negative rate; If mitochondrial disease is suspected, refer the patient to a mitochondrial disease center.
Clinical Laboratory “red flags” for mitochondrial disease

**Blood tests**
- Elevated lactate
- Lactate/pyruvate ratio >20
- Amino acids: elevated alanine

**Urine**
- Organic acids
  - Elevated tricarboxylic acid (TCA) cycle intermediates
  - Elevated 3-methylglutaconic acid
  - Elevated lactate
Diagnostic Evaluation

IMAGING TESTING

- Bilateral deep gray [putamen, GP, caudate]
- Metabolic stroke [non-vascular territory]
- Diffuse white matter abnormalities
- Lactate on MRS (abnl choline, NAA)
- Cerebral and/or cerebellar volume loss

Leigh  MELAS  KSS  ETC def MNGIE MERRF
Screening for mitochondrial diseases

When should I consider ordering a muscle biopsy?

- CPEO phenotype to screen for single or multiple deletions of mtDNA
- mtDNA variant of uncertain significance (VUS) to look for mitochondrial defects that confirm pathogenicity
- Infantile-onset myopathy/SMA-like phenotype to screen for mtDNA depletion
- Strongly suspect a mitochondrial disease but genetic screening is negative
Diagnostic Evaluation

EM

Histochemistry

RRF

COX

SDH
Screening for mitochondrial diseases

Muscle biochemical assays

"Frozen" Spectrophotometric assays versus "Fresh" Polarographic assays

Assesses complexes I-IV and citrate synthase

Measures activities of complexes I-V


DiMauro et al. Mitochondrial Medicine 2006

Courtesy of Dr. Michio Hirano
Screening for mitochondrial diseases

Muscle biochemistry

Western blot analyses

Blue native gel and 2-dimensional analyses of mitochondrial enzyme complexes


Nijtmans et al. Methods 2002;26:327-34

Courtesy of Dr. Michio Hirano
Diagnostic Evaluation

Molecular Testing: New Gold standard

- mtDNA
  - Screen point mutations
  - Whole genome screen
  - Deletion/duplication analysis
  - Depletion
Screening for mtDNA diseases

Which tissue should I screen?
• For mtDNA point mutations: use blood or urine

TABLE I. Proportion (percent) of A3243G Mutation in Five Tissues From 12 Different Patients

<table>
<thead>
<tr>
<th>Patient number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>5</td>
<td>30</td>
<td>ND</td>
<td>57</td>
<td>14</td>
<td>11</td>
<td>55</td>
<td>65</td>
<td>3</td>
<td>16</td>
<td>13</td>
<td>40</td>
</tr>
<tr>
<td>Urine</td>
<td>84</td>
<td>88</td>
<td>11</td>
<td>98</td>
<td>67</td>
<td>84</td>
<td>63</td>
<td>92</td>
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<td>98</td>
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<tr>
<td>Mucosa</td>
<td>35</td>
<td>61</td>
<td>17</td>
<td>71</td>
<td>52</td>
<td>46</td>
<td>69</td>
<td>73</td>
<td>14</td>
<td>37</td>
<td>17</td>
<td>63</td>
</tr>
<tr>
<td>Fibroblasts</td>
<td>22</td>
<td>47</td>
<td>56</td>
<td>59</td>
<td>40</td>
<td>66</td>
<td>97</td>
<td>45</td>
<td>ND</td>
<td>18</td>
<td>24</td>
<td>73</td>
</tr>
<tr>
<td>Hair 1</td>
<td>ND</td>
<td>42</td>
<td>45</td>
<td>71</td>
<td>74</td>
<td>22</td>
<td>85</td>
<td>83</td>
<td>10</td>
<td>50</td>
<td>7</td>
<td>38</td>
</tr>
<tr>
<td>Hair 2</td>
<td>7</td>
<td>37</td>
<td>ND</td>
<td>9</td>
<td>22</td>
<td>59</td>
<td>69</td>
<td>63</td>
<td>3</td>
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<td>Hair 3</td>
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<td>27</td>
<td>71</td>
<td>36</td>
<td>9</td>
<td>18</td>
<td>11</td>
<td>51</td>
</tr>
</tbody>
</table>


Courtesy of Dr. Michio Hirano
Diagnostic Evaluation

Molecular Testing: New Gold standard

- mtDNA
  - Screen point mutations
  - Whole genome screen
  - Deletion/duplication analysis
  - Depletion

- nDNA
  - Specific gene selection
  - Screening – NGS
    - panel
    - whole exome/whole genome or dual genome analysis
Screening for mitochondrial diseases

Nuclear DNA sequencing

**Mito panel sequencing**

**Pros**
Excellent coverage of nDNA genes known to cause mitochondrial diseases.

**Cons**
Does not cover all nDNA genes

**Whole exome sequencing (WES)**

**Pros**
Unbiased sequencing of ~90-95% of coding regions of all nDNA genes.

Detects mutations in non-mitochondrial genes

**Cons**
May miss mutations in regions of poor sequence coverage.

Mito panel sequencing is better when the clinical phenotype or lab tests indicates a specific set of likely genes while WES is preferred for patients with non-specific clinical and lab features.
Biomarkers

- FGF21
- DGF15
The Management

• Symptomatic
  • End organ survey and treatment

• Supportive
  • Overall disease burden

• Non curative
Typical treatment: Symptomatic

**Nutritional Management**
- Enteral vs. parenteral nutrition
- Special formulas/diets
- GT/JT

**Symptomatic Treatments**
- Avoid dehydration
- Electrolyte abnormalities
- Annual Neurology exam
  - Avoid valproic acid
  - MRI, EEG, EMG
- Annual Cardiologist exam (KSS)
  - Prophylactic pacemakers
  - Avoid dehydration
  - Electrolyte abnormalities
- Nutrition (enteral vs. parenteral)
- Special formulas/diets
- GT/JT

**Other Treatments**
- Annual Cardiologist exam (KSS)
- Prophylactic pacemakers
- Avoid dehydration
- Electrolyte abnormalities

**Ocular Treatments**
- Annual ophtho exam
  - Prisms, slings
  - Blepharoplasty
  - Sleep disturbances and apnea, polysomnography

**Renal Treatments**
- Annual screen

**Endocrine Treatments**
- Annual screen
  - AFT
  - Hearing evaluation

**Cardiac Treatments**
- Conduction abnormalities
- Cardiomyopathy: hypertrophic, dilated

**Musculoskeletal Treatments**
- Myopathy
  - Skeletal muscle-ocular
  - axial/proximal > buttock > distal muscles
  - Smooth muscle: dysphagia
  - Cardiac/cardio-myopathy
  - Myalgia

**Gastrointestinal Treatments**
- Dysphagia
  - Dysmotility, gastroparesis, diarrhea, constipation, and/or pseudo-obstruction
  - Hepatic failure

**Neurologic/Peripheral Treatments**
- Acute polyneuropathy
  - Sensory ataxia
  - Sensory/motor hearing loss
  - Autonomic dysfunction
Treatment and Management

Exercise

Typical treatment: Supportive

- Hydration
- Diet adjustments
Typical treatment: Supportive

• Palliative Care Team
• Early Intervention
• Social worker, case manager
• Support Groups, etc.
Typical treatment: Supportive

• Avoid environmental toxins:
  • ETOH
  • Smoking
  • Certain medications
<table>
<thead>
<tr>
<th>Medication</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid</td>
<td>Hepatopathy; infrequently direct encephalopathy</td>
</tr>
<tr>
<td>Antiretrovirals</td>
<td>Peripheral neuropathy, liver dysfunction, myopathy</td>
</tr>
<tr>
<td>Statins</td>
<td>Myopathy</td>
</tr>
<tr>
<td>Aminoglycoside antibiotics</td>
<td>Hearing loss, cardiac toxicity, renal toxicity</td>
</tr>
<tr>
<td>Aminoglycoside and platinum chemotherapeutics (Doxirubicin)</td>
<td>Hearing loss, cardiac toxicity, renal toxicity</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Hepatopathy</td>
</tr>
<tr>
<td>Metformin</td>
<td>Lactic acidosis</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Reduced exercise tolerance</td>
</tr>
<tr>
<td>Steroids</td>
<td>Reports of deterioration in Kearns-Sayre syndrome</td>
</tr>
</tbody>
</table>
Episodic Phenotype

Stress →

TIME
OBSERVABLE
DYSFUNCTION

normal
mild
aging

Organ Failure

severe

moderate
Typical treatment

• Avoid physiologic stressors:

  Infection (treat early, control fevers)
  Heat (hydration, cooling vest, avoidance)
  Fasting (minimize)
  Lack of sleep
Typical treatment

- Dietary Supplements (The Mito Cocktail)

What makes sense?
Mitochondrial replacement therapy

Gorman et al. Nature reviews primers 2016
Ressources
MMS Papers (links to journal articles open in a new window)

1. MMS Consensus Criteria on Diagnosis and Treatment of Mitochondrial Disease – Genetics in Medicine
2. Practical Approach for the PCP - Pediatrics
3. Management of Stroke in MELAS - JAMA Neurology
4. Outcomes after solid organ transplantation in Primary Mitochondrial Disease - Molecular Genetics & Metabolism
5. Practice Patterns of Mitochondrial Medicine Physicians in North America – Part 1 - diagnostic and clinical care challenges - Mitochondrion
6. Practice Patterns of Mitochondrial Medicine Physicians in North America – Part 2 - treatment and management concerns - Mitochondrion

Older Publications (for newer information see the publications above)

1. The In-Depth Evaluation including how to interpret metabolic studies, tissue testing, what to send on the muscle biopsy and how to begin a genetic evaluation
2. A modern approach to the treatment of mitochondrial disease
3. Illness management table referenced in treatment article

Diagnostic & Consensus Criteria (links to journal articles open in a new window)

1. MMS Consensus Criteria on Diagnosis and Treatment of Mitochondrial Disease – Genetics in Medicine
2. Nijmegen Group Mitochondrial Disease Criteria (MDC)
3. Bernier & Thorburn

Parent/Patient/Physician Handouts (links to pdf's open in a new window)
Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society

Sumit Parikh, MD1, Amy Goldstein, MD2, Mary Kay Koenig, MD3, Fernando Scaglia, MD4, Gregory M. Enns, MD5, Russell Saneto, MD, PhD6,7, Irina Anselm, MD8, Bruce H. Cohen, MD9, Marni J. Falk, MD10, Carol Greene, MD11, Andrea L. Gropman, MD12, Richard Haas, MB Chir, MRCP13, Michio Hirano, MD14, Phil Morgan, MD15, Katherine Sims, MD16, Mark Tarnopolsky, MD, PhD17, Johan L.K. Van Hove, MD18, Lynne Wolfe, MS, CRNP19 and Salvatore DiMauro, MD20

Review
May 2016

Recommendations for the Management of Strokelike Episodes in Patients With Mitochondrial Encephalomyopathy, Lactic Acidosis, and Strokelike Episodes

Mary Kay Koenig, MD1; Lisa Emrick, MD2; Amel Karaa, MD3; et al.

► Author Affiliations | Article Information

I know Mito. Do you?
Share your story!
Post your photos and videos of how you know Mito.

#iknowmito
#iknowmito
Welcome To The North American Mitochondrial Disease Consortium

Mitochondrial diseases are a challenge because they are probably the most diverse human disorders at every level: clinical, biochemical, and genetic. Although severity varies, by and large these are progressive and often crippling disorders. The NAMDC, working closely with the United Mitochondrial Foundation (UMDF), is working to address these difficult issues.
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United Mitochondrial Disease Foundation
Muscular Dystrophy Association
MitoAction
• Thank you, and any questions?