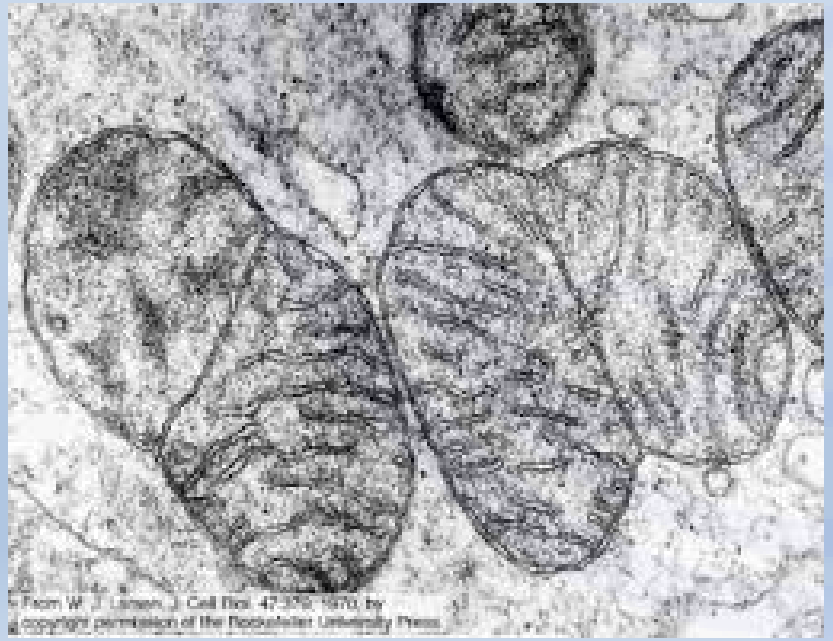
Mitochondrial Disorders



Irina Anselm, MD
Mitochondrial Program
Department of Neurology
Boston Children's Hospital

Disclosures

- No relevant financial relationships to disclose

DS1

Objectives

- Clinical presentation of children and adolescents with mitochondrial disorders
- Evaluation of children and adolescents with suspected mitochondrial disorders
- Therapeutic interventions for children and adolescents with mitochondrial disorders
- Controversies and misperceptions about mitochondrial disorders

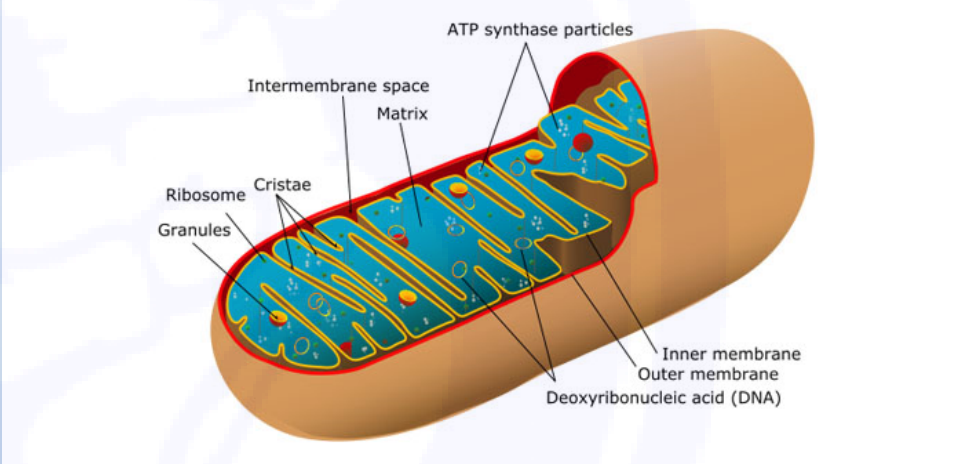


Image by Mariana Ruiz Villarreal

Slide 3

DS1

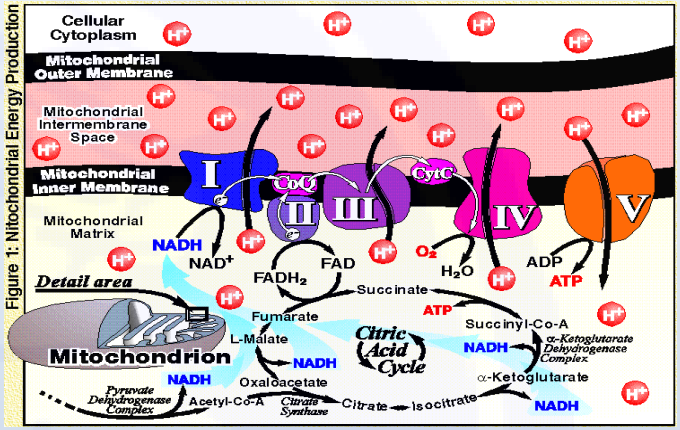
This image looks decorative. If so, suggest using a version without the labels, so that viewers don't think they need to digest the imate.
This image is in the public domain: https://commons.wikimedia.org/wiki/File:Animal_mitochondrion_diagram_unlabelled.svg
Dan Schwartz, 8/27/2020

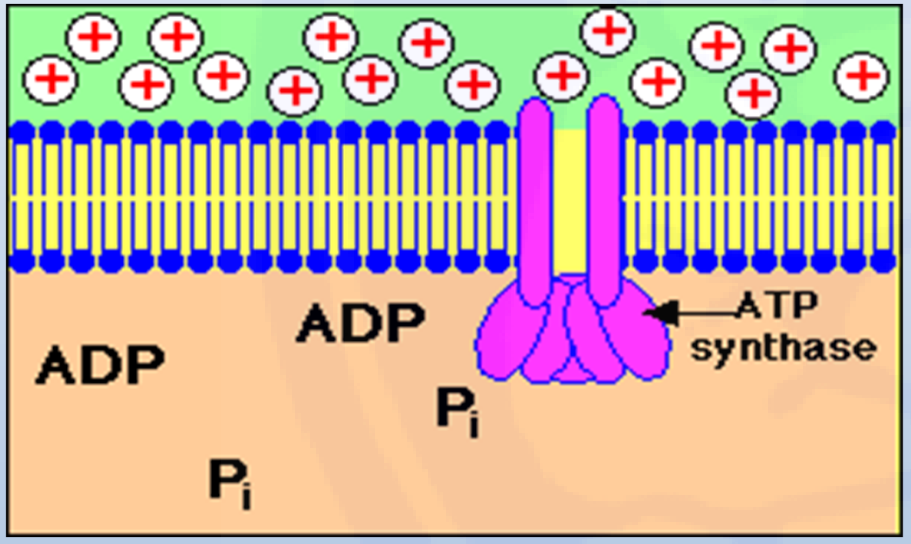
DS2
DS5

Mitochondrial functions

Energy production

Oxidation-Phosphorylation





- Fatty Acid Oxidation
- Pyruvate metabolism
- Krebs cycle
- ROS generation
- Programmed cell death/ apoptosis
- Ca++ homeostasis
- Heme synthesis
- Steroid metabolism

http://www.mammag.uci.edu/foswiki/bin/view/MAMMAG/PhilosophicalPremiseOfMAMMAG

http://cmapspublic.ihmc.us/rid=1102536487930_333741980_4083/ATPanim.gif

Slide 4

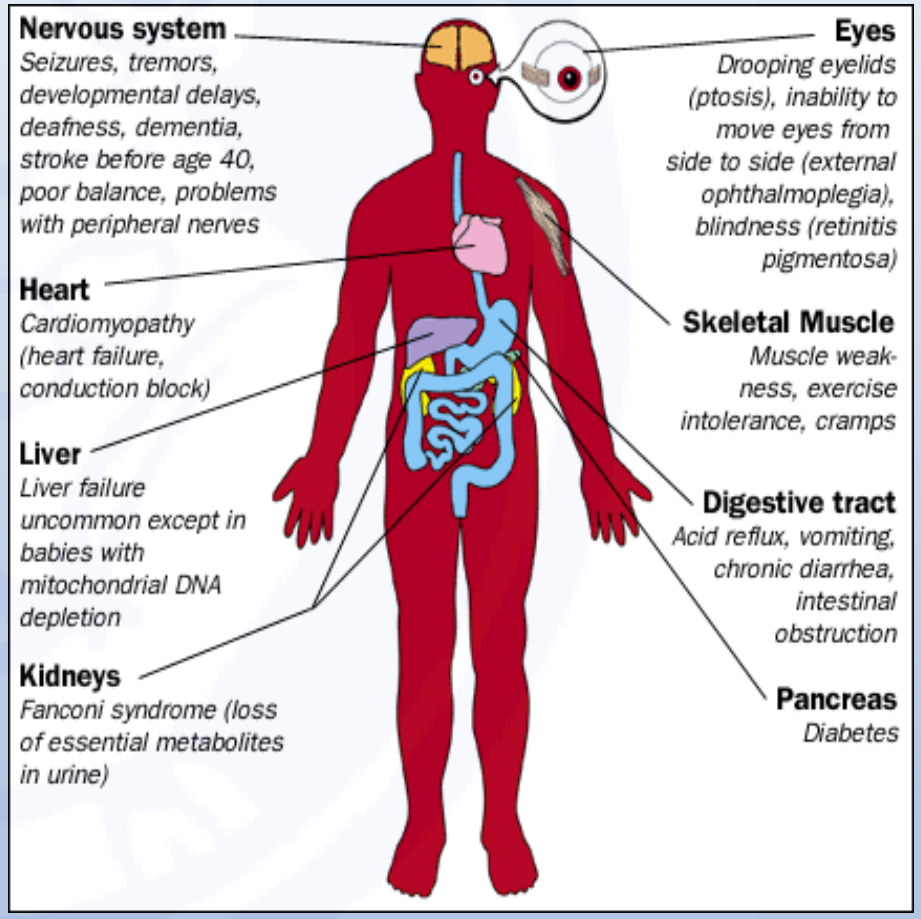
DS2 There is a lot going on on this slide, beteen the two graphics. Suggest breaking the slide into to 2, so that each graphic stands alone. This would also allow for enlarging the graphics. The graphic in the upper right is particularly difficult to read. Also, why treat the fatty acid oxidation text in gray? If viewers are to read it, suggest keeping it black.
Dan Schwartz, 8/27/2020

DS5 Broken link: http://www.mammag.uci.edu/foswiki/bin/view/MAMMAG/PhilosophicalPremiseOfMAMMAG
Dan Schwartz, 8/27/2020

DS3
DS4

Mitochondrial Disorders

- Arise as a result of dysfunction of the mitochondrial respiratory chain
- Disorders impacting the structure or function of the mitochondria
- Tissues and organs that are highly dependent on aerobic metabolism are affected the most



Source: Mitochondria Research Society

Slide 5

DS3 Suggest removing the graphic in the upper right corner. At that size it is illegible.
Dan Schwartz, 8/27/2020

DS4 This image is easily reproduced if rights or permission has not been obtained.
Dan Schwartz, 8/27/2020

Mitochondrial Disorders

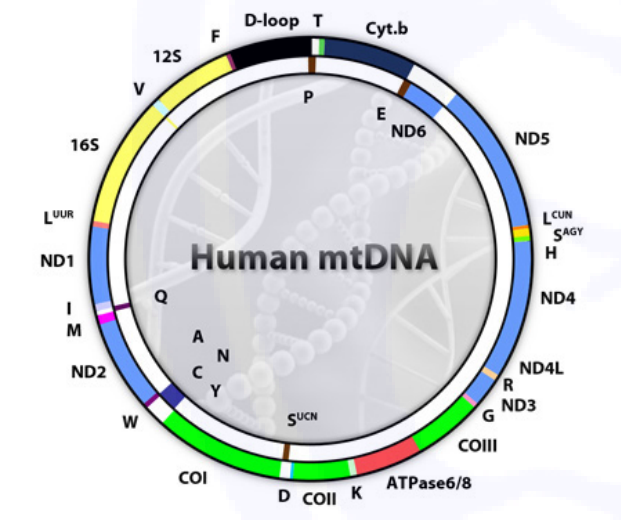
"Any symptom, any organ, any age, any mode of inheritance"

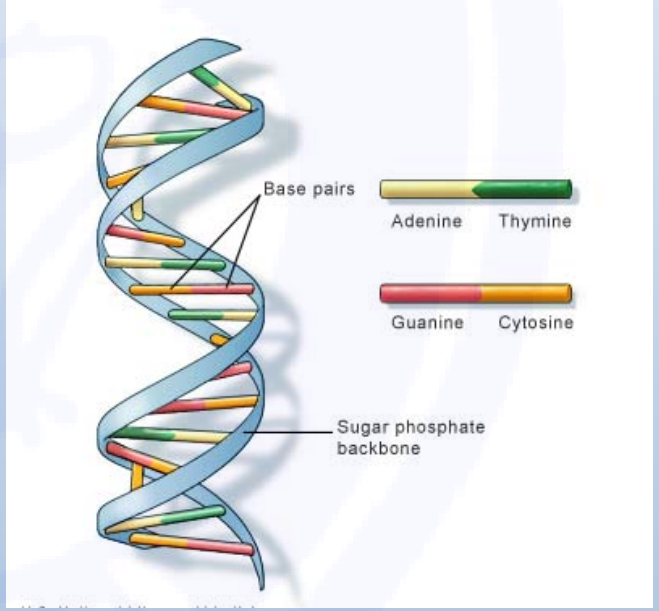
- Munnich & Rustin (Am.J.Med.Genet. 2001, 106:4-17)

- Hundreds of different diseases
- Different combination of symptoms
- Many genes causing the same disease
- The same gene can cause many different types of MDs
- Neurological symptoms are very common, especially in children with MDs

Prevalence of Mitochondrial Disorders

- At least 1 in 4,300 of adults will develop mitochondrial disease





Source: The Mariani Foundation Center for the Study of Pediatric Mitochondrial Diseases, hosted by the Molecular Neurogenetics Unit of the IRCCS Foundation Neurological Institute "C. Besta" at Bicocca
http://www.mitopedia.org/eng/img/mitocondri2_z.jpg

U,S, National Library of Medicine

Slide 7

DS8 If this image can subsitute, is has a creative commons license:
https://en.wikipedia.org/wiki/Human_mitochondrial_genetics#/media/File:Mitochondrial.svg

Emmanuel Douzery CC BY-SA 4.0
Dan Schwartz, 8/27/2020

Gorman GS, et al.

Prevalence of Nuclear and Mitochondrial DNA Mutations Related to Adult Mitochondrial Disease

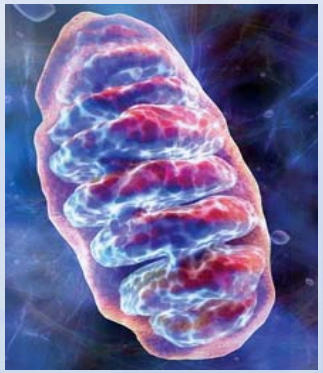
- "Combined, our data confirm that the total prevalence of adult mitochondrial disease, including pathogenic mutations of both the mitochondrial and nuclear genomes (1 in 4,300), is among the commonest adult forms of inherited neurological disorders."

- " These figures hold important implications for the evaluation of interventions, provision of evidence-based health policies, and planning of future services. "

ANN NEUROL 2015;77:753–759

Controversies and misperceptions about mitochondrial disorders (MDs)

- MDs are rare
- Inherited from mothers
- Can be diagnosed clinically
- Can be diagnosed on muscle biopsy
- Untreatable
- Unpreventable



https://www.google.com/search?q=mitochondrial+division&biw

Slide 9

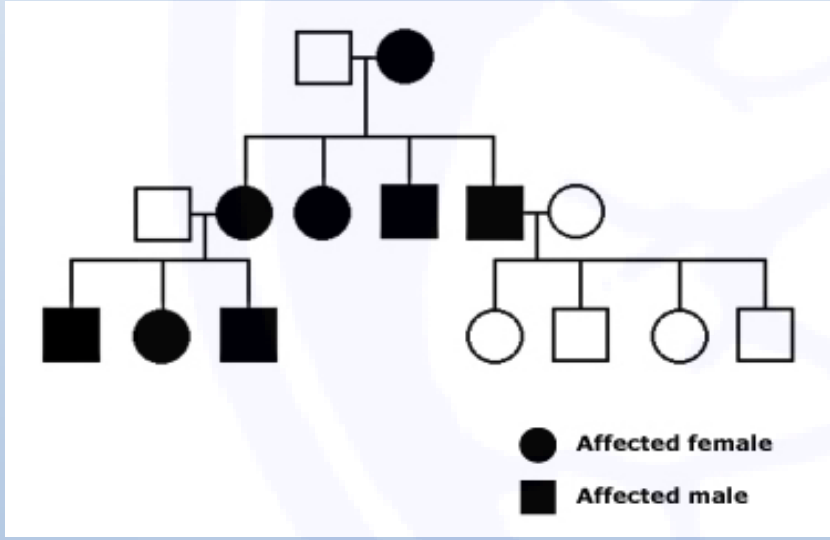
DS7 If these imeages are just decorative, and are not necessary to convey information or illustrate concnepts, suggest removing them. They distractfrom the text.

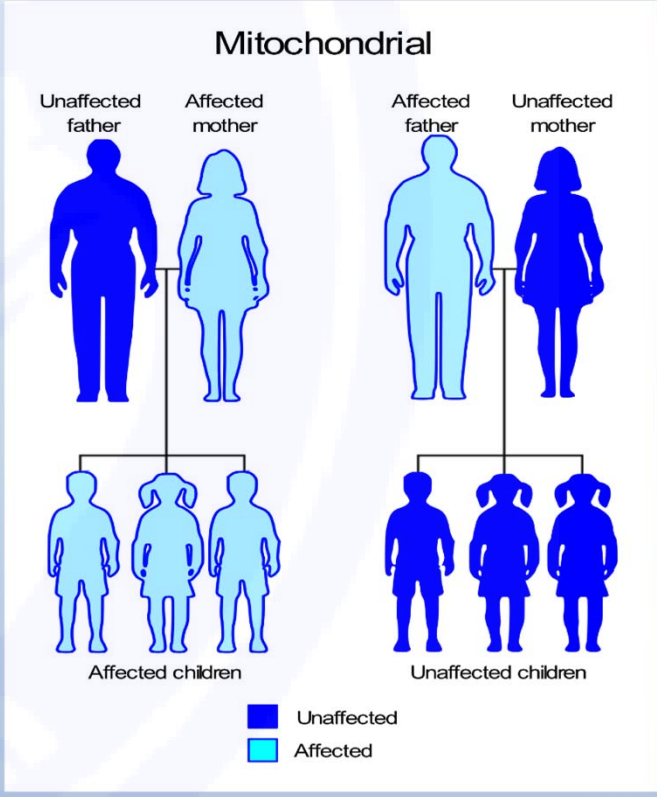
Dan Schwartz, 8/27/2020

DS9

"Inherited from mothers" Inheritance of MDs

- Maternal **MELAS, MERRF, Leigh Disease**





https://en.wikipedia.org/wiki/Human_mitochondrial_genetics#/media/File:Mitochondrial.svg

DS10

Slide 10

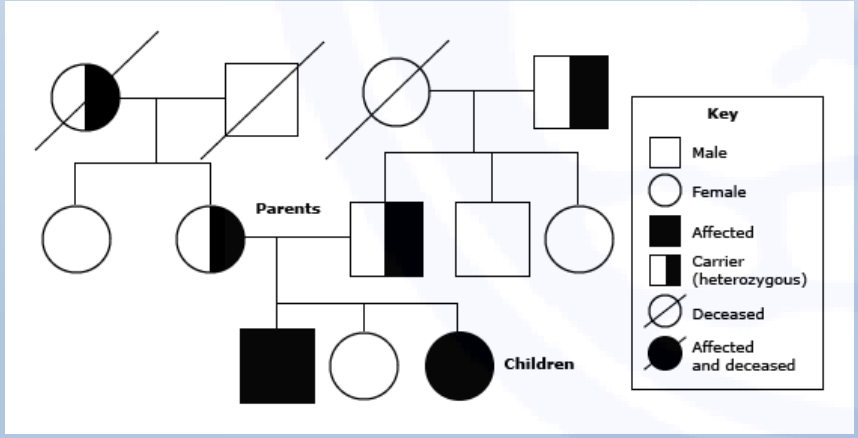
DS9 The graphic in the upper left corner is illegible, i sit necessary? If not, suggest removing it.
Dan Schwartz, 8/27/2020

DS10 And are the other two images illustrating the same basic concept? If so reomove one (suggest the image with the human figures is more intuitive.)
But note that the image at the URL on the slide is different than either of the images on the slide. The URL has a similar version of the affected/unaffected figures, with a creative commons license.
CC BY-SA 4.0
If replacing, be sure to click on the image at the URL to download the larger version.
Dan Schwartz, 8/27/2020

Inheritance of Mitochondrial Disorders

Mitochondria are under dual control from mtDNA and nuclear DNA

Around 1400+ nuclear genes are involved in proper mitochondrial function



Maternal MELAS, MERRF, Leigh
Autosomal recessive Leigh, POLG
Autosomal dominant POLG
X-linked PDC deficiency
Sporadic Kearns Sayre syndrome

"If organelles could talk," available at: www.beatricebiologist.com

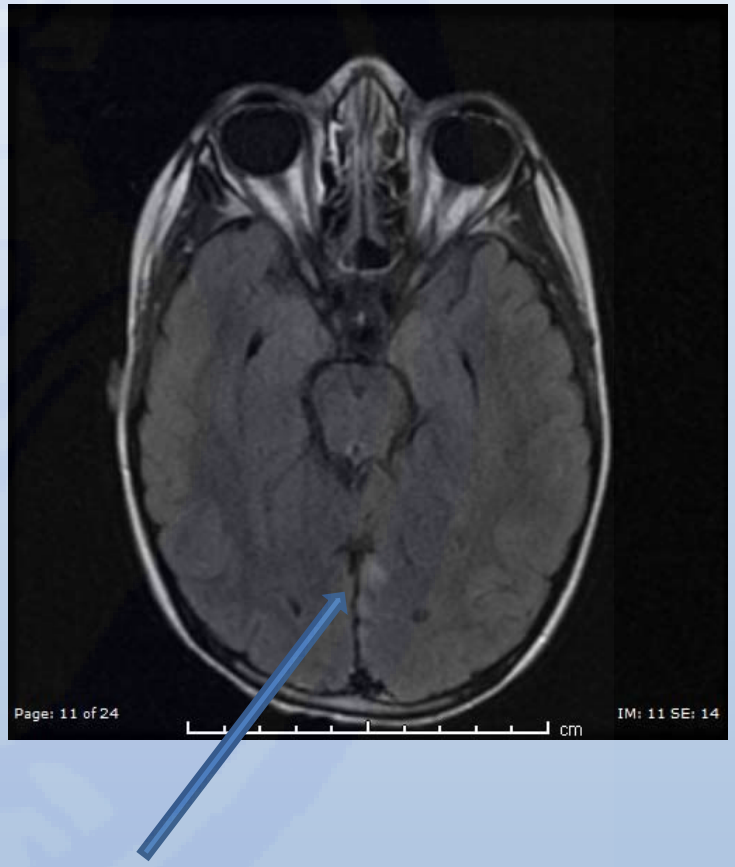
Slide 11

DS11 The organelle cartoon is from an illustrator who sells products with the image, and is clearly copyrighted. Suggest removing, unless permission is obtained. Or, could launch the image from the illustrators web site: http://www.beatricebiologist.com/2014/03/if-organelles-could-talk/

Also consider enlarging the image bottom left corner, non eo fthe text is legible.
Dan Schwartz, 8/27/2020

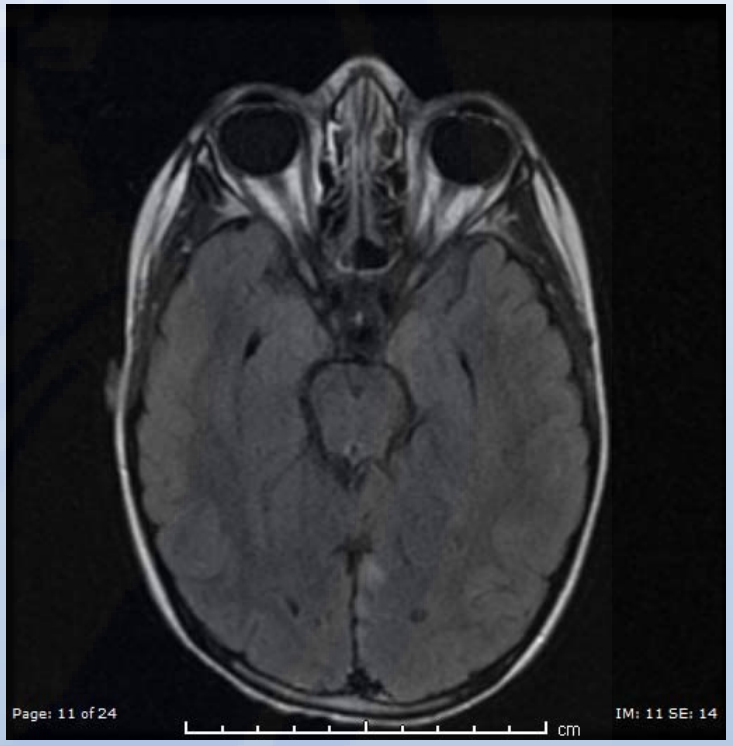
Patient TA

- 8-year-old boy
- History of mild gross motor delay presents with generalized seizures and visual hallucinations, consisting of geometrical figures
- Hallucinations persist for several weeks
- High blood lactate and pyruvate
- Diagnosis?



Patient TA

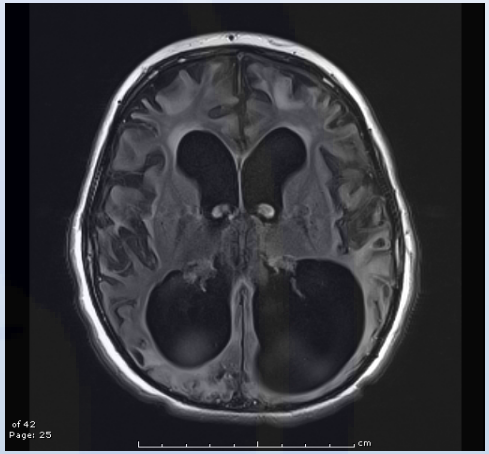
Diagnosed with **MELAS**
(mitochondrial encephalomyopathy, lactic acidosis, stroke like episodes)
due to classical mutation
(m.3243A>G)



Subsequently he has many seizures, develops EPC (epilepsia partialis continua), gradual loss of vision, progressive quadriparesis and dies at age 13 years

MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, Stroke-like episodes)

- Described in 1984
  - Stroke-like episodes before age 40
  - Encephalopathy with dementia, seizures or both
  - Lactic acidosis (blood or CSF), RRF or both



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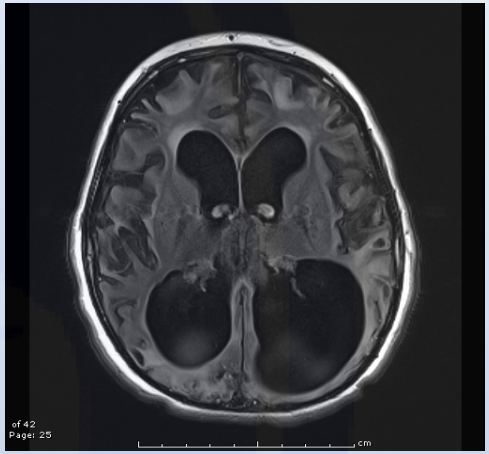

Neurosensory hearing loss
Migraine headaches
Peripheral neuropathy
Myopathy with ragged red fibers (RRF)
Seizures, epilepsy partialis continua (EPC)
Depression and other psychiatric disorders
Dementia

MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, Stroke-like episodes)

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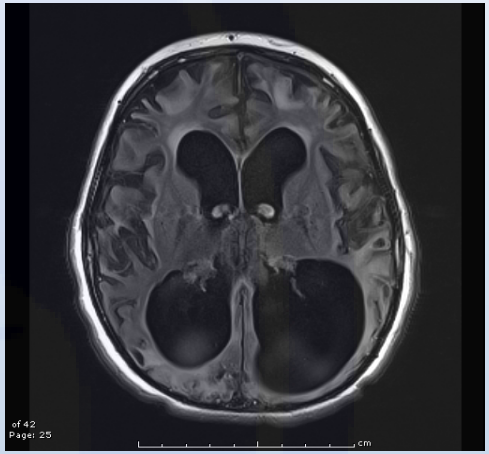


Neurosensory hearing loss

Migraine headaches

Peripheral neuropathy

Myopathy with ragged red fibers (RRF)

Seizures, epilepsy partialis continua (EPC)

Depression and other psychiatric disorders

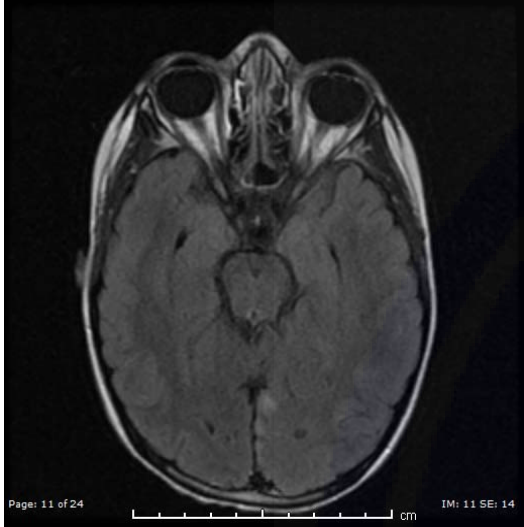
Dementia

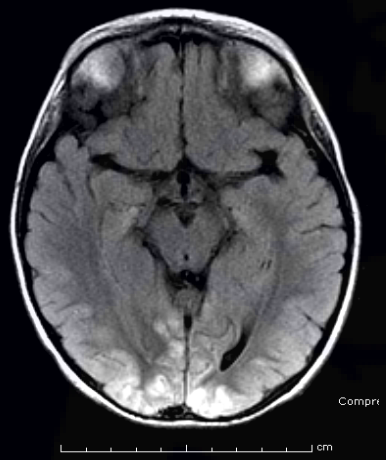
Endocrine: diabetes, growth failure, gonadal dysfunction, hypothyroidism

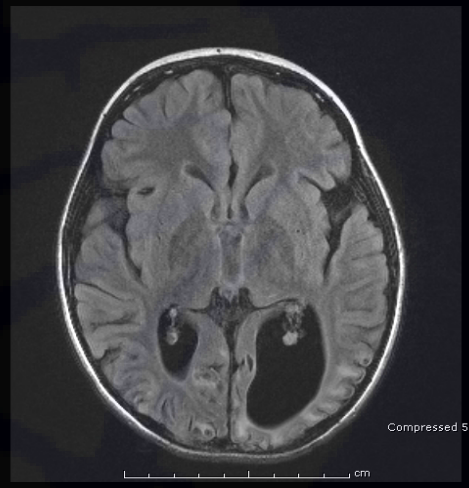
Cardiac involvement: hypertrophic or dilated cardiomyopathy, ventricular arrhythmias, conduction block

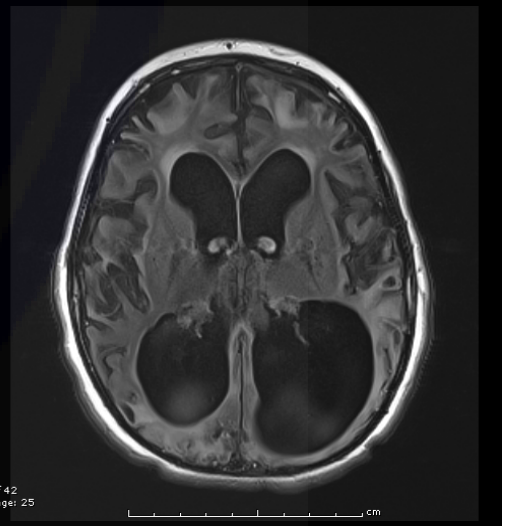
Kidney dysfunction/failure

Progression of brain atrophy in MELAS

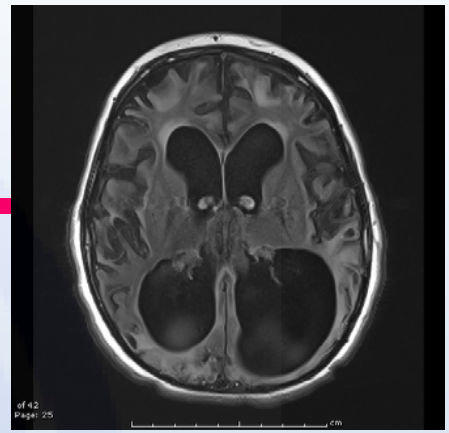








MELAS



- **Always due to mutations in mtDNA**

- **80%** of cases are caused by mutations in **MT-TL1 gene** in mtDNA encoding tRNA leucine 1, $tRNA^{Leu(UUA/UUG)}$ **(m.3243A>G)**

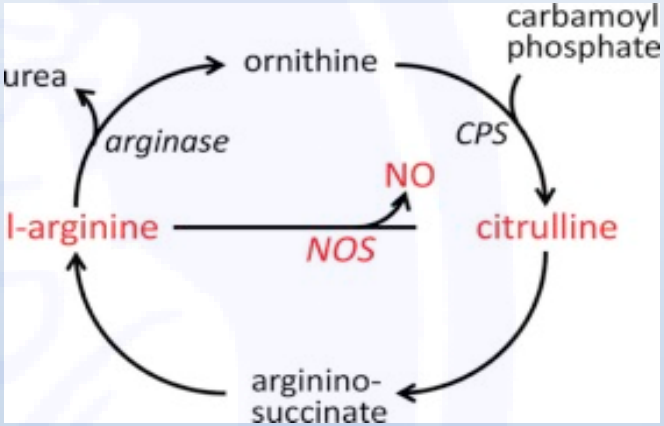
  ~7.5% m.3271T>C

  <5% m.3252A>G

- **Other mtDNA genes:** Mutations known to cause MELAS have been identified in other mtDNA tRNA genes including *MT-TC, MT-TK*, *MT-TV, MT-TF, MT-TQ*, *MT-TS1, MT-TS2*, and *MT-TW,* and in the protein-encoding genes *MT-CO1, MT-CO2, MT-CO3*, *MT-CYB*, *MT-ND1*, *MT-ND3*, and *MT-ND6*

Arginine and Citrulline for the Treatment of MELAS Syndrome

Nitric Oxide (NO) deficiency can play a major role of the pathogenesis of stroke like episodes



Supplementation of **NO precursors, arginine and citrulline**, can result in increased NO availability and have therapeutic effects

Arginine IV during stroke like episode **0.5 g/kg/day**

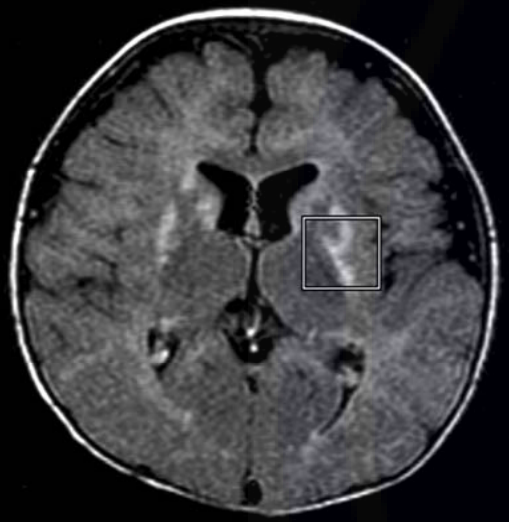
Citrulline supplementation can raise NO production to a greater extent than that associated with **arginine**

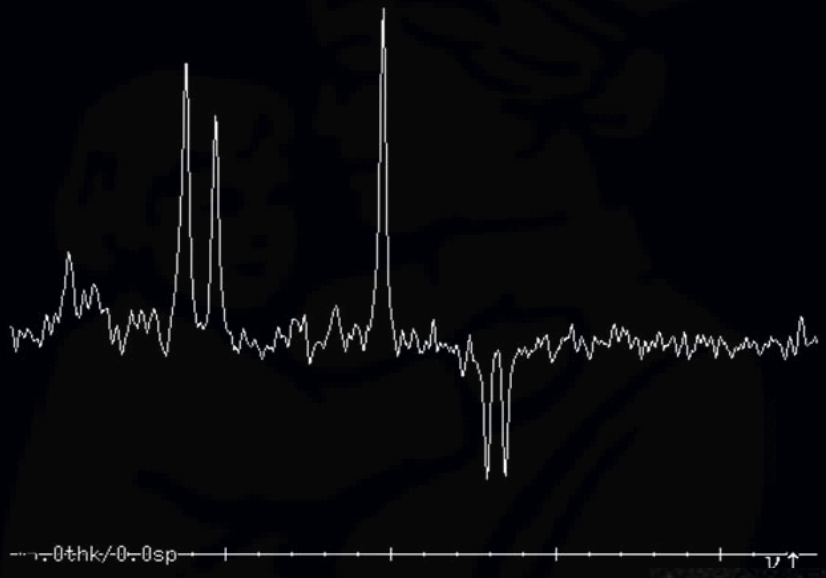
As prophylaxis **0.15-0.3 g/kg/day**

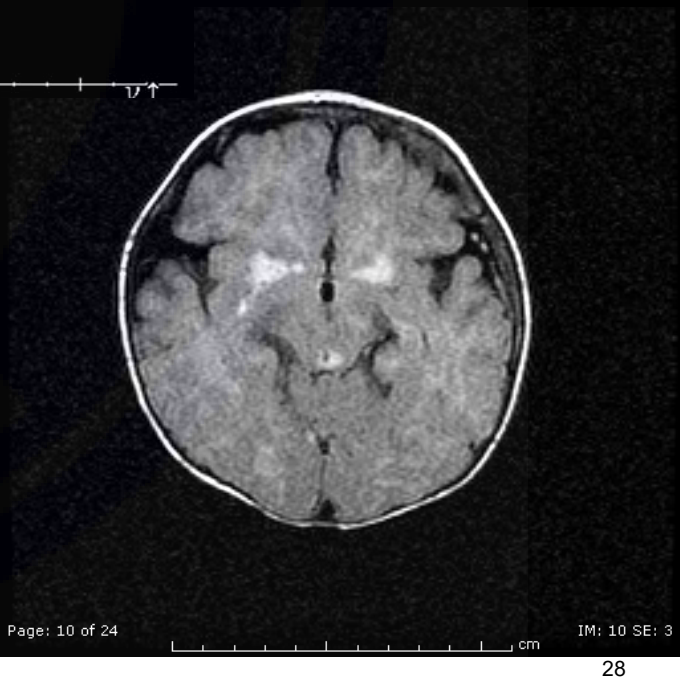
Patient SM

- 10-month-old boy presents with gross motor delay, severe hypotonia and generalized weakness
- Birth history unremarkable
- High blood lactate, low CO2, normal CPK, normal blood and urine amino acids and urine organic acids

Patient SM

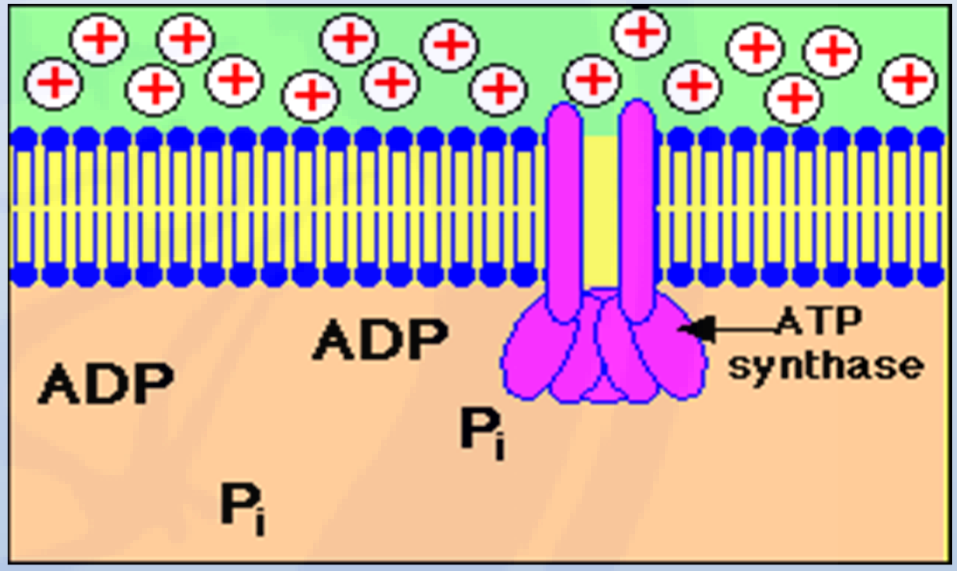






- MRI and MRS findings compatible with mitochondrial disease such as **Leigh disease**

- Confirmed by **mitochondrial DNA** analysis of the blood: 8993 T>G (Heteroplasmy 88%), ATPase gene mutation



Complex V

Schon EA et al. *Semin Cell Dev Biol.* 2001;12(6):441-448

Schon EA, Santra S, Pallotti F, Girvin ME. *Semin Cell Dev Biol 2001;12(6):441-448*

Slide 22

DS14 The image in the upper right corner is illegible. Suggest remvoing.
Dan Schwartz, 8/27/2020

Leigh Syndrome

Obituaries

Denis Archibald Leigh. *formerly Consultant Psychiatrist, Maudsley Hospital, Denmark Hill, London*

Noble P. Psychiatric Bulletin 1998;22(10):648-9

J. Neurol. Neurosurg. Psychiat., 1951, **14**, 216.

SUBACUTE NECROTIZING ENCEPHALOMYELOPATHY IN AN INFANT

BY

DENIS LEIGH

From the Department of Neuropathology, Institute of Psychiatry, Maudsley Hospital, London

The following case appears to be unique in that no references to a similar condition can be found in the literature. In addition it merits consideration as an example of the reaction of the infant brain to disease.

Case Report

K.H., a boy, aged 7 months 3 weeks, was admitted to King's College Hospital on April 22, 1947.

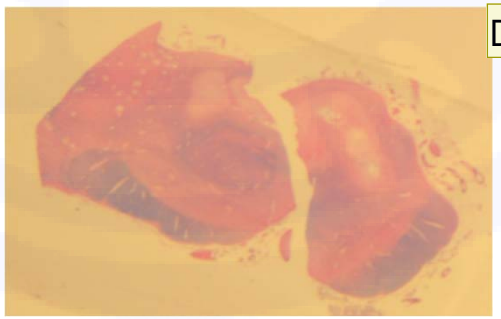
Birth had been normal (birth weight 6¾ lb.) as also was development until six weeks before admission. The infant was vaccinated at the age of 2 months. He was breast-fed entirely for six weeks, then complementary feeding was begun.

The child became rapidly worse, and on April 25 was comatose, dying in terminal hyperpyrexia later the same day.

The clinical diagnosis was obscure, but an encephalitic process was considered to be the most likely cause of the fatal illness.

Necropsy.—A necropsy was performed 69 hours after death. No abnormality was observed except in the central nervous system.

The brain weighed 740 g. There was a severe, diffuse vascular injection of the leptomeninges. The convolutions were normal in size and appearance. In coronal sections the cerebral white matter seemed somewhat greyer than normal. The left lateral ventricle was



DS15

Spongy Lesions in Rostral Midbrain

Image courtesy of Dr. Hart Lidov

Slide 23

DS15 There is a lot going on here visually. Could each image be treated on a separate slide, which would allow the spongy lesions image to be enlarged.

Dan Schwartz, 8/27/2020

Leigh Disease/syndrome

- Psychomotor retardation
- Hypotonia, weakness
- Dystonia, chorea
- Ptosis, oculomotor disturbances
- Optic atrophy, retinitis pigmentosa
- Lactic acidosis (blood, CSF)

Leigh Disease/syndrome

- Psychomotor retardation
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Cardiac – hypertrophic cardiomyopathy

Hepatic – liver failure

Renal – renal tubular acidosis

Pulmonary – respiratory abnormalities

GI – failure to thrive

Leigh Disease/syndrome

- Psychomotor retardation
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- Lactic acidosis (blood, CSF)

Cardiac – hypertrophic cardiomyopathy

Hepatic – liver failure

Renal – renal tubular acidosis

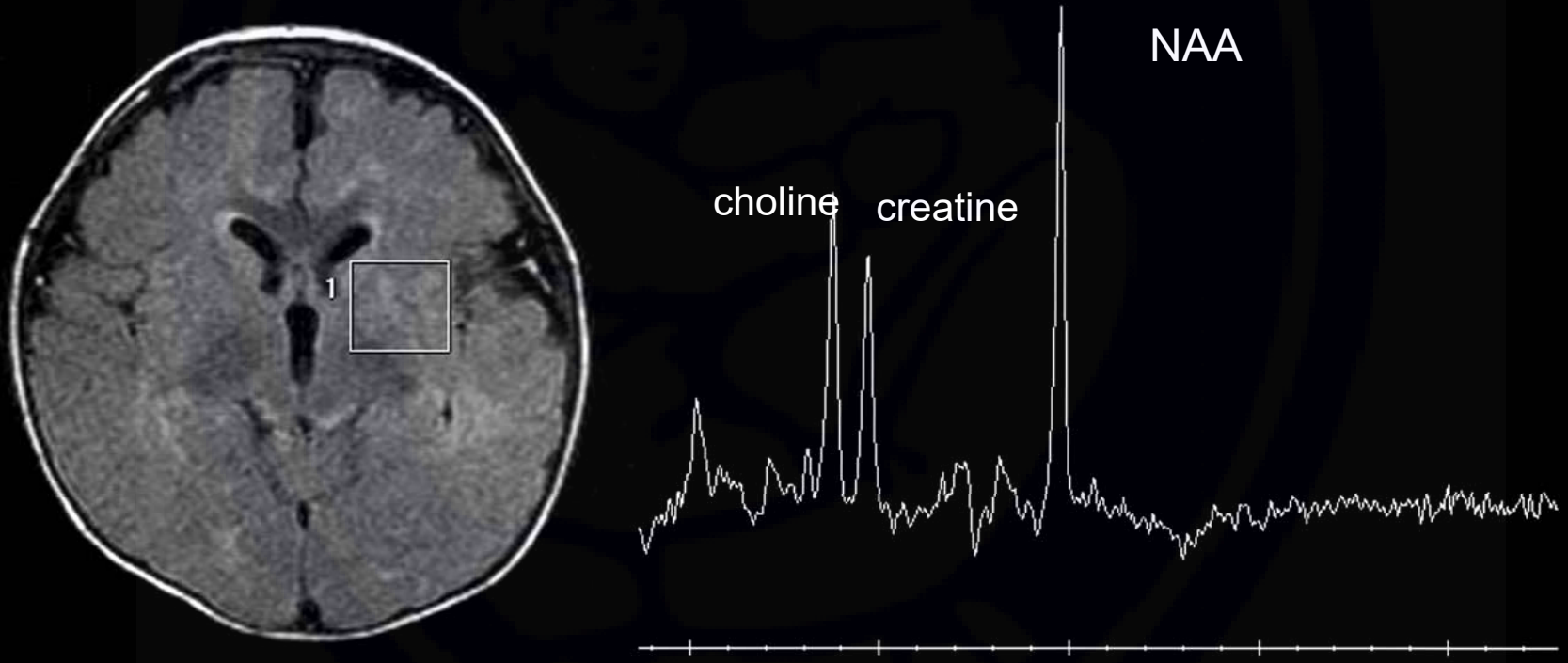
Pulmonary – respiratory abnormalities

GI – failure to thrive

Always a mitochondrial disorder with defect of oxidative phosphorylation

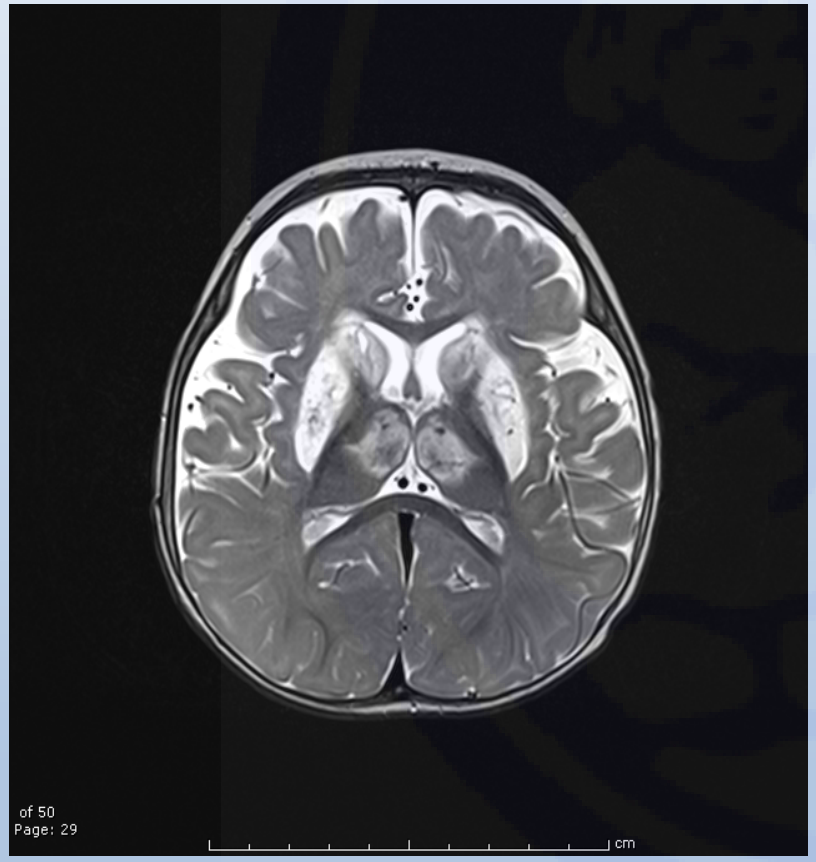
May be due to mutations in mitochondrial and nuclear DNA

Patient SM Several years after original MRI



7-month-old with developmental delay, laryngomalacia, feeding difficulty, increased muscle tone

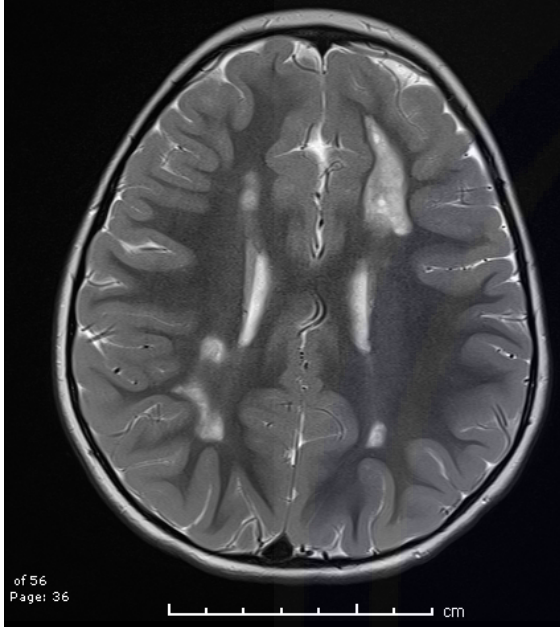
- High blood lactate and pyruvate, low CO2 12, high CSF lactate

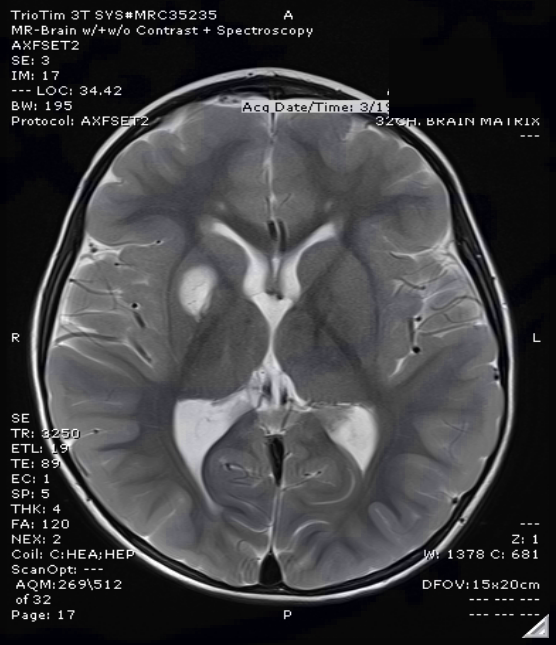


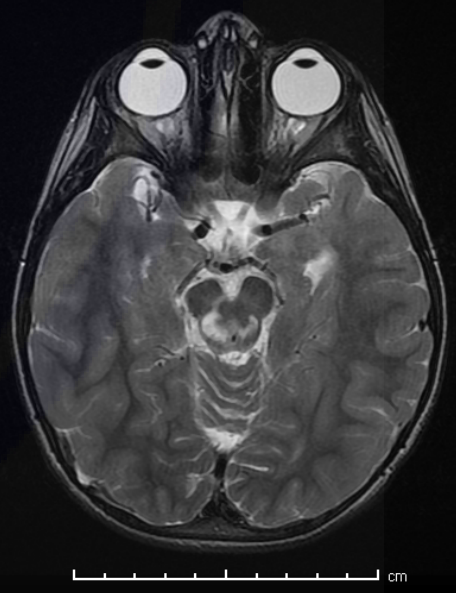
Mitochondrial DNA: **negative**

WES: Compound heterozygous mutations in **NDUFAF3 gene** that encodes the protein that is involved in the assembly of complex I of the mitochondrial electron transport chain

Leigh and Leigh like disease







Approach to suspected mitochondrial disorders

- **Clinical assessment**

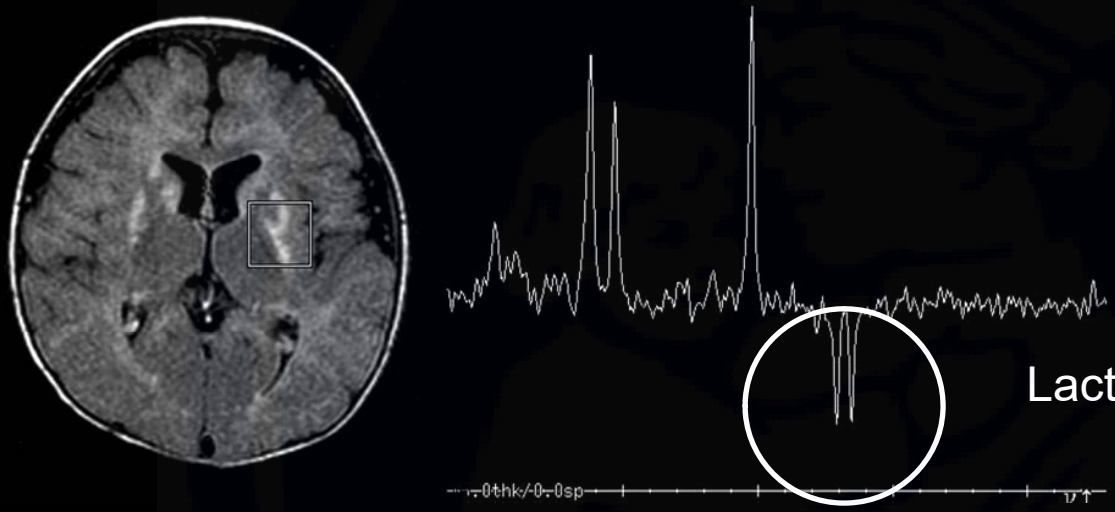
- **Metabolic screening on blood**
- Chem10: low bicarb, increased AG
- Elevated lactate, pyruvate, L/P ratio
- Blood amino acid: elevated alanine
- GDF15

- **Urine organic acid**
- TCA intermediates, 3-methyl glutaconic acid, lactate

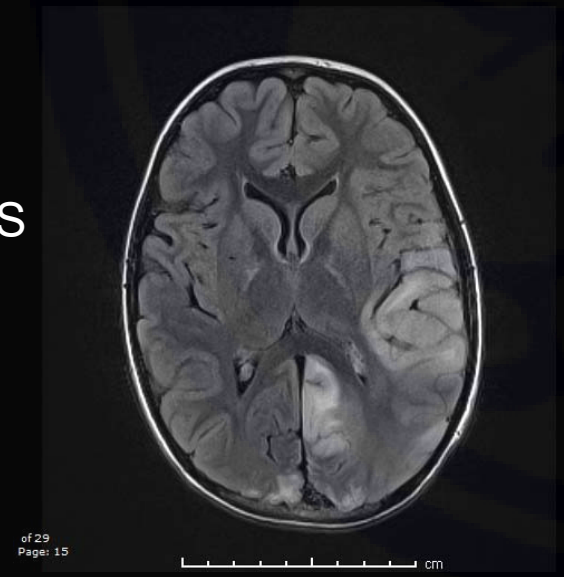
- **CSF analysis**
- lactate, amino acids, folate

Approach to suspected mitochondrial disorders

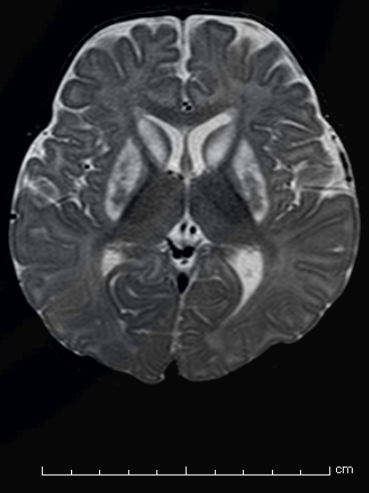
Brain MRI, MR spectroscopy



MELAS



Leigh disease



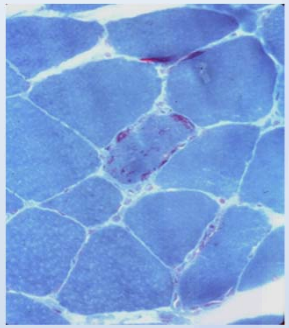
Approach to suspected mitochondrial disorders

- **Molecular testing**

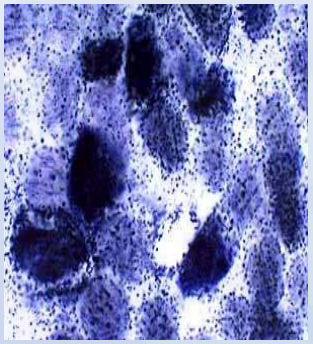
- **Mitochondrial DNA**
  - Sequence analysis of the entire mitochondrial genome with quantification of heteroplasmy levels
  - Detection of deletions with breakpoints and heteroplasmy

- **Nuclear DNA ("mitome" genes)**
  - Next generation (NGS) panels (up to 1100 genes)
  - Whole exome (genome)sequencing

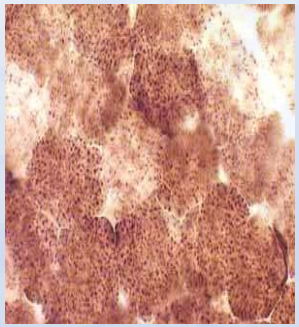
Muscle Biopsy



RRF

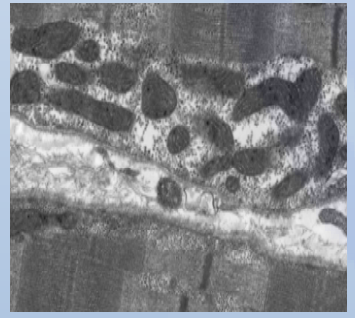


RBF

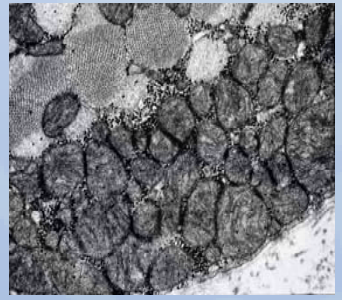


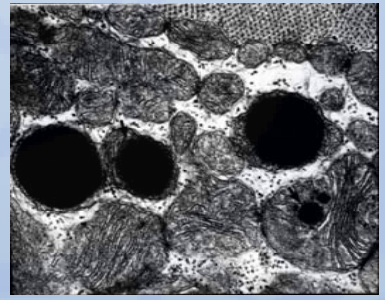
COX normal

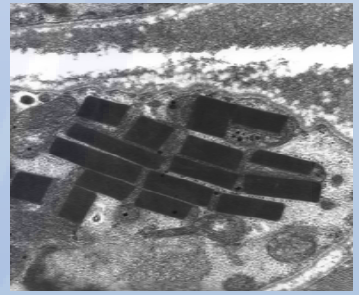
COX negative fibers



Normal



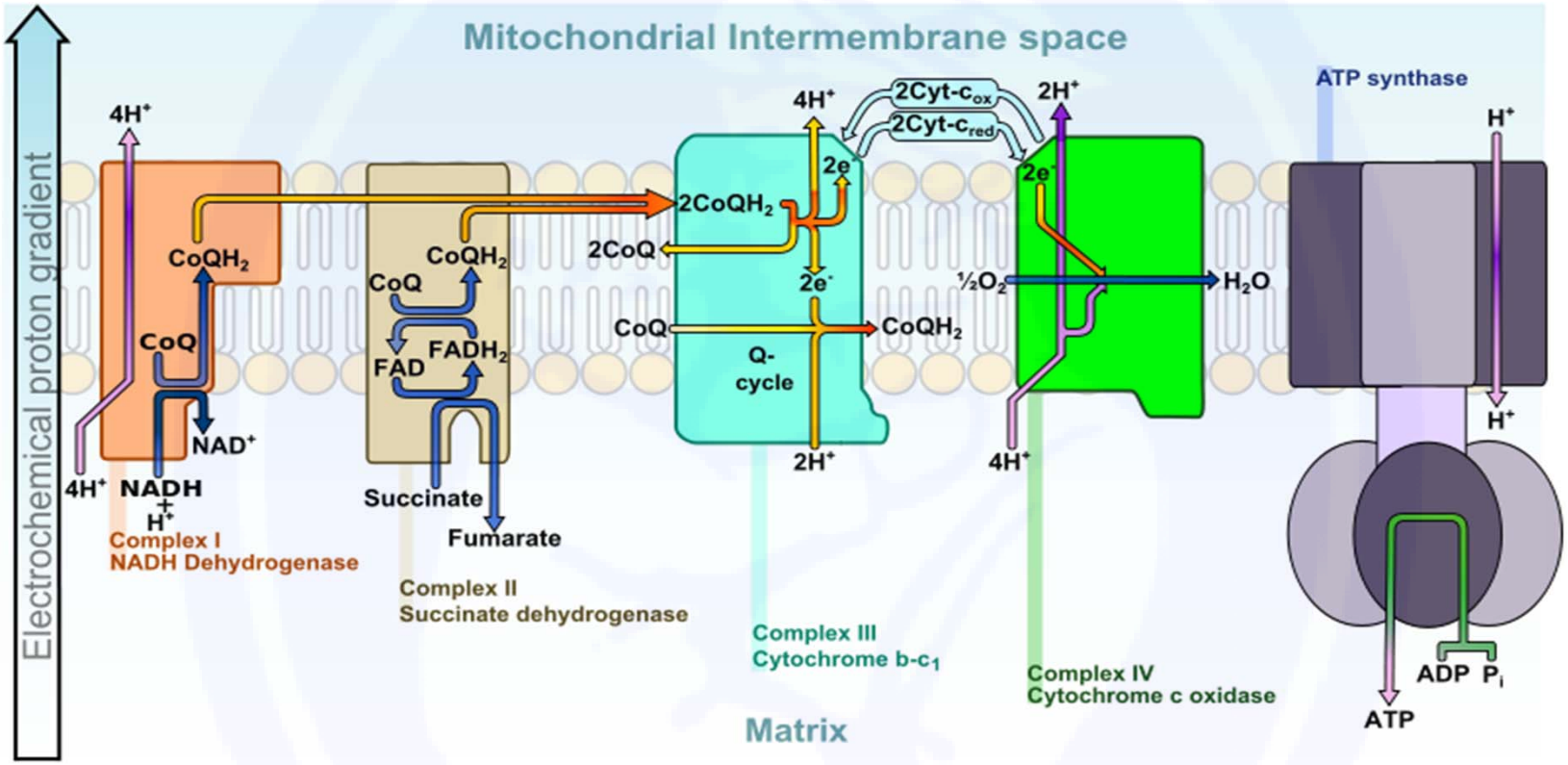




Intra mitochondrial inclusions

Images courtesy of Basil T. Darras, MD

"Complex Deficiency"



Parikh S, et al. **Diagnosis of 'possible' mitochondrial disease: an existential crisis.** J Med Genet. 2019 Mar;56(3):123-130

http://commons.wikimedia.org/wiki/File:ETC_electron_transport_chain.svg

Slide 34

DS16 Enlarge image if possible, text is difficult to read.
Dan Schwartz, 8/27/2020

DS17

Mitochondrial Disorders and Munchhausen by Proxy

Slide 35

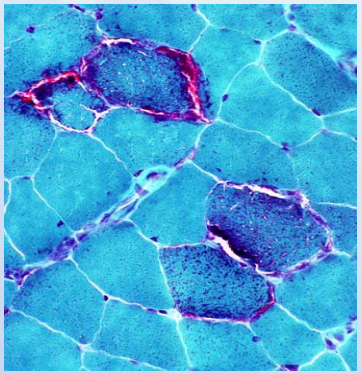
DS17 Google search URL is not the actual URL for the image, so doesn't quality as a citation.
Dan Schwartz, 8/27/2020

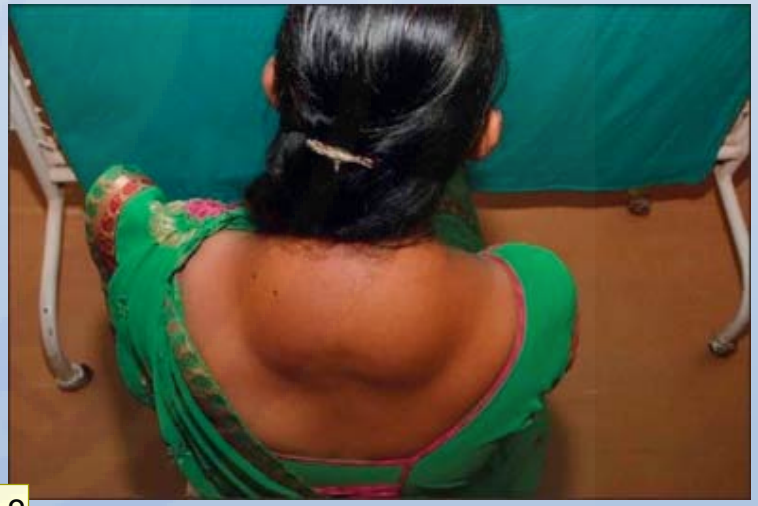
Patient EF

- 5 year old boy with normal development is found to have decreased hearing
- Myoclonic seizures and ataxia
- Brain MRI unremarkable
- Severe malnutrition
- Dies at age 9 years

Myoclonic Epilepsy Associated with Ragged Red Fibers (MERRF)

- Myoclonus, generalized epilepsy, ataxia, weakness, and dementia
- Additional manifestations:
  - failure to thrive/short stature
  - hearing loss
  - cardiomyopathy
  - multiple lipomas
  - >80% caused by mutations in *MT-TK* of m.8344A>G





DS18
DS19

https://commons.wikimedia.org/wiki/File:Ragged_red_fibres_-_gtc_-_very_high_mag.jpg

Finsterer J., Zarrouk-Mahjoub S., Shoffner J.M. MERRF Classification: Implications for Diagnosis and Clinical Trials, Pediatric Neurology. 2018;80: 8-23,

Slide 37

DS18 Use this image if applicable because it has creative commons license:
https://commons.wikimedia.org/wiki/File:Ragged_red_fibres_-_gtc_-_very_high_mag.jpg
Nephron CC BY-SA 3.0
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DS19 Sitatin for bottom image is:
Finsterer J., Zarrouk-Mahjoub S., Shoffner J.M. MERRF Classification: Implications for Diagnosis and Clinical Trials, Pediatric Neurology. 2018;80: 8-23,
Dan Schwartz, 8/27/2020

Kearns-Sayre Syndrome

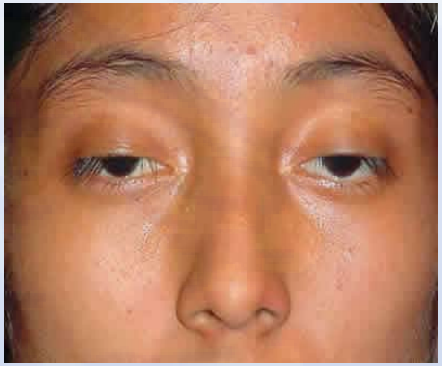
- CPEO
- Ptosis
- Retinal degeneration

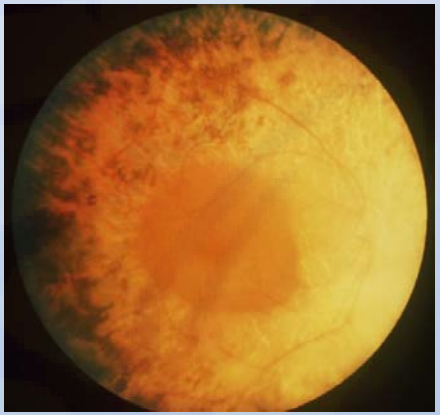
- Other features
  - Cerebellar ataxia
  - Hearing loss
  - Complete heart block
  - Elevated CSF protein
  - Endocrinopathies

    diabetes

    hypoparathyroidism

    adrenal insufficiency



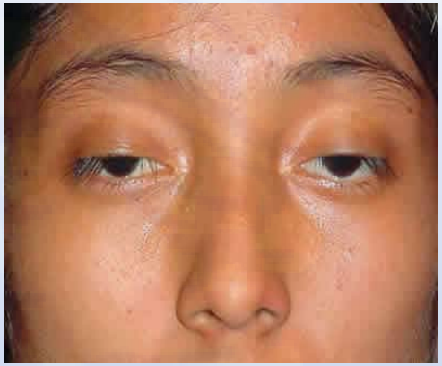


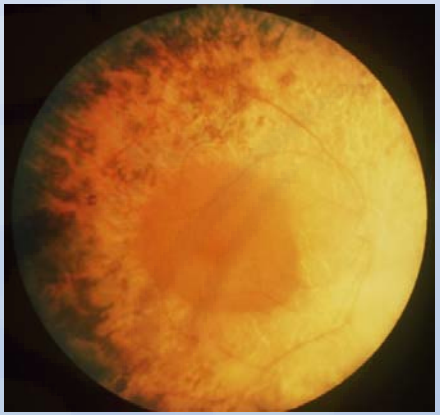
Top: Ramírez-Miranda A et al. Arch Soc Esp Oftalmol 2008;83(3)
Bottom: Telander DG. Retinitis Pigmentosa. Medscape 2017.
https://emedicine.medscape.com/article/1227488-overview

Kearns-Sayre Syndrome

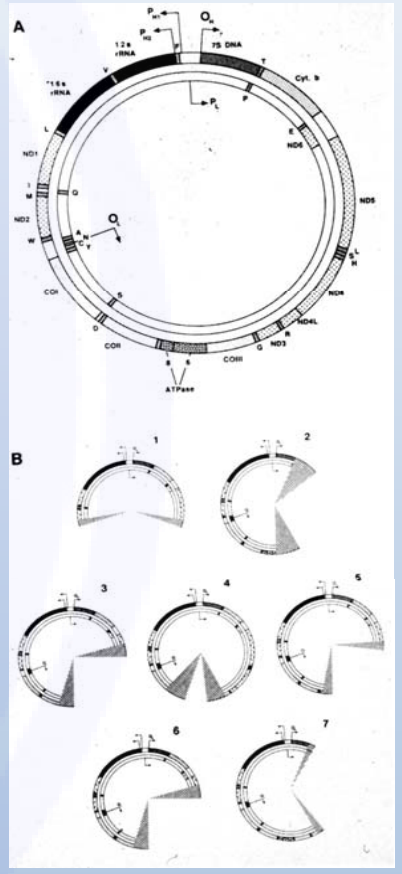
- CPEO
- Ptosis
- Retinal degeneration

- Other features
  - Cerebellar ataxia
  - Hearing loss
  - Complete heart block
  - Elevated CSF protein
  - Low CSF folate
  - Endocrinopathies
    diabetes
    hypoparathyroidism
    adrenal insufficiency





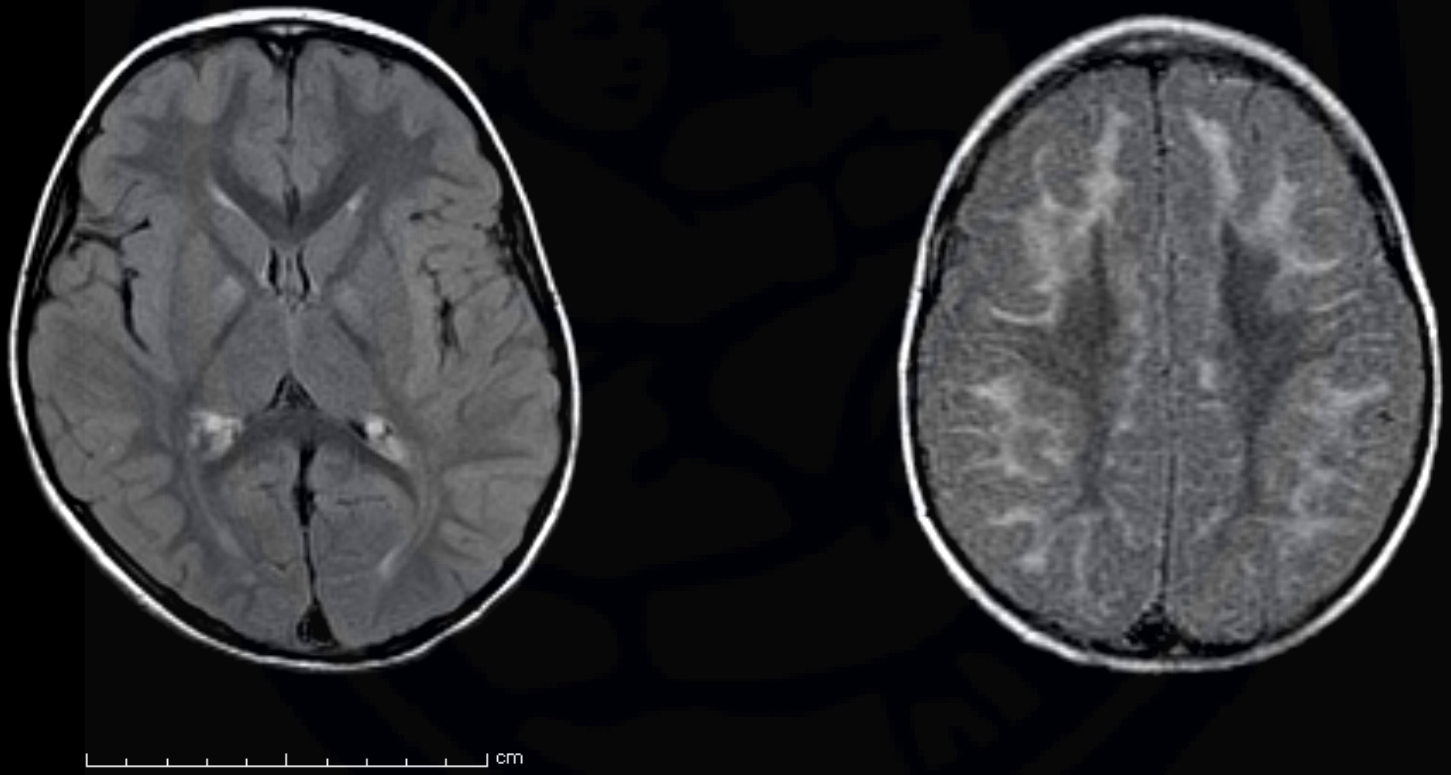
MtDNA deletions



Nearly always sporadic

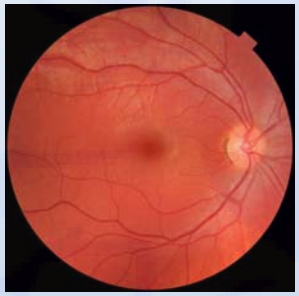
Top: Ramírez-Miranda A et al. Arch Soc Esp Oftalmol 2008;83(3)
Bottom: Telander DG. Retinitis Pigmentosa. Medscape 2017. https://emedicine.medscape.com/article/1227488-overview
Right: Zeviani M et al. Neurology 1998;51(6)

Kearns Sayre Syndrome (KSS)



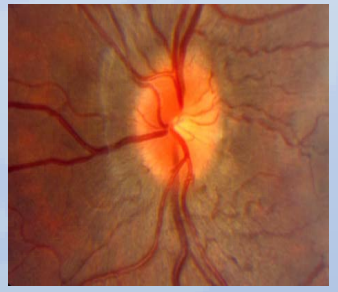
Leber Hereditary Optic Neuropathy (LHON)

- Bilateral, painless, subacute visual failure during young adult life
- Males are 4 to 5 times more likely than females to be affected
- Visual field testing shows an enlarging dense central or centrocecal scotoma
- Approximately 90% of individuals with LHON have one of three point mutations of mtDNA: m.3460G>A, m.11778G>A, or m.14484T>C



Normal fundus

http://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/normal-fundus.htm



Minimal disc swelling and peripapillary telangiectatic vessels in LHON

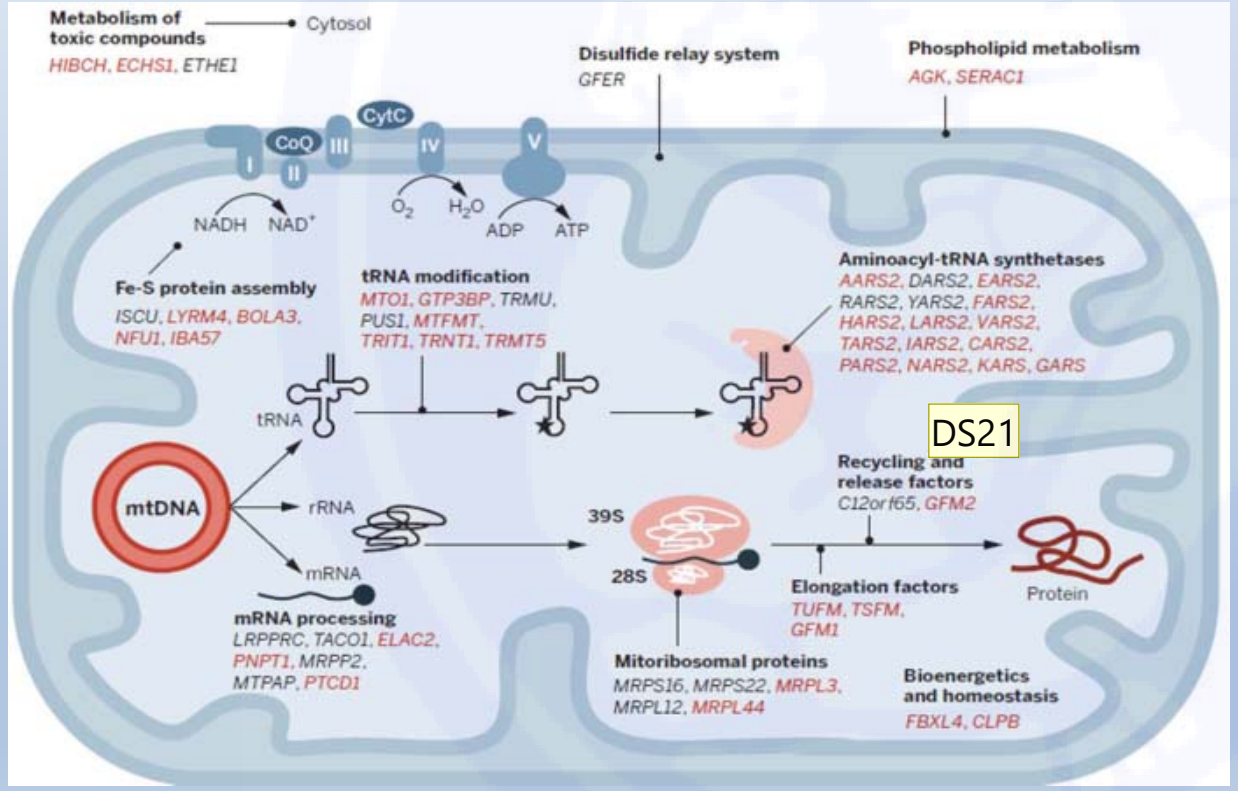
Slide 41

DS20 Suggest enlarge images

Dan Schwartz, 8/27/2020

Mitochondrial Disorders due to Nuclear Gene Mutations

Around 1400+ nuclear genes are involved in proper mitochondrial function



Role of nuclear "mito" genes

- Structural subunits of ETC complexes
- Assembly of ETC complexes
- Intergenomic signaling between nDNA and mtDNA
- Mitochondrial replication/biogenesis
- Mitochondrial assembly & stability
- Mitochondrial membrane synthesis
- Mitochondrial fusion & fission

Science VOL 349 ISSUE 6255

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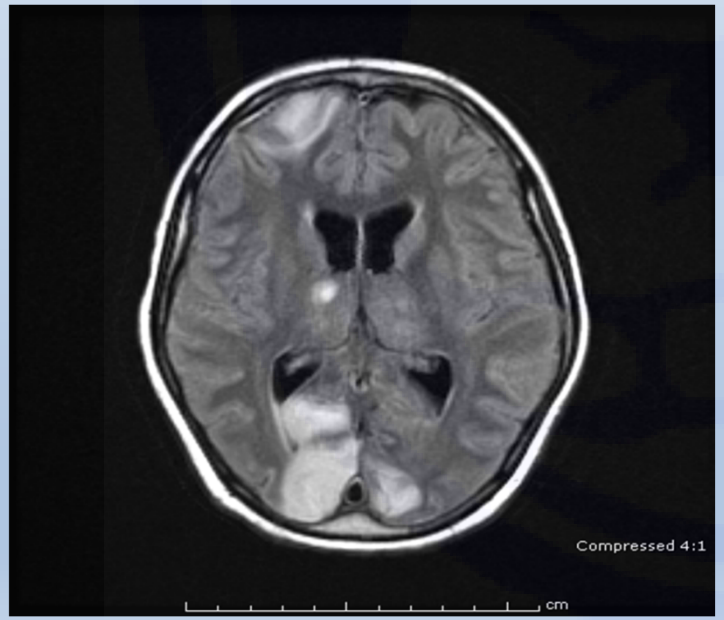
DS21 This is illegible at current size. If it's important information, suggest enlarging and de-emphsizing or removing text
Dan Schwartz, 8/27/2020

Patient TP

- 12-year-old boy with history of moderate global developmental delay, hypotonia, GI dysmotility and seizures



- Fresh muscle biopsy at age 3 years; low activity of Complex I
- Over the years blood lactate normal, metabolically stable
- At age 12 had increase in seizure frequency, developed continuous facial and arm twitching
- Placed in a phenobarbital coma and never regained consciousness
- Remained in a vegetative state for 6 months until his death from respiratory complications

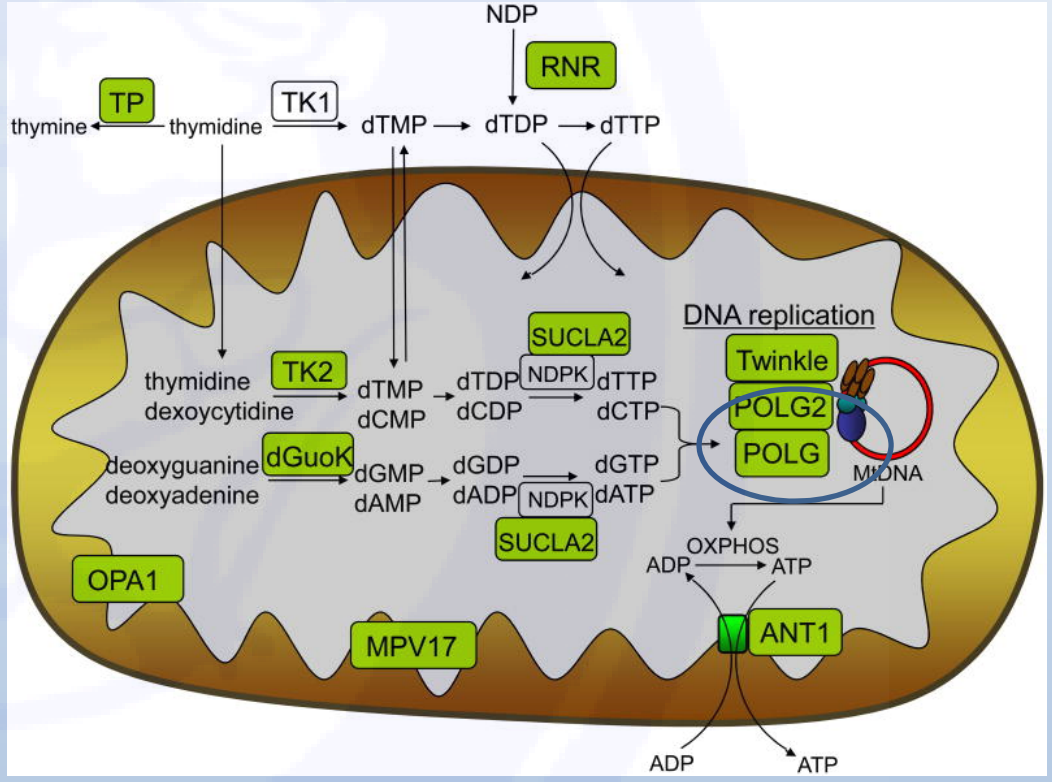
Patient TP

- **Two heterozygous mutations in POLG1 (Polymerase Gamma 1) c.911T>G and c.3433_3434insGGAG**

- "Both mutations are deleterious and are confirmative of the affected status of the patient"

POLG Disease

- Autosomal Dominant Syndrome
  - AD progressive external ophthalmoplegia (PEO)
- Autosomal Recessive Syndromes
  - Myocerebrohepatopathy syndrome
  - Alpers syndrome
  - Ataxia neuropathy spectrum syndrome
  - Myoclonus, Epilepsy, Myopathy and Sensory Ataxia
  - AR PEO



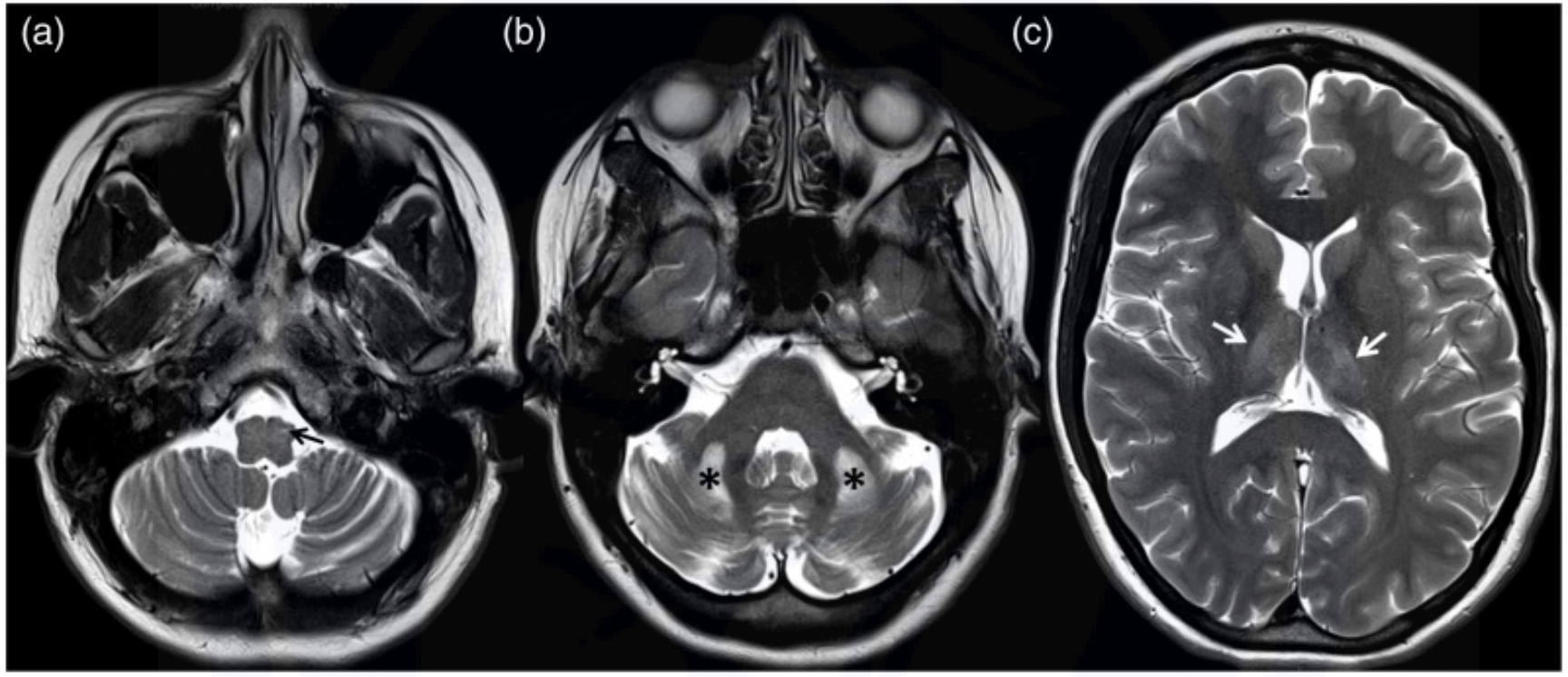
Chan SS, Copeland WC. *Biochim Biophys Acta 2009 May;1787(5):312-9.*

Slide 45

DS22 Hard to read image, suggest enlarging

Dan Schwartz, 8/27/2020

MRIs in patients with POLG related

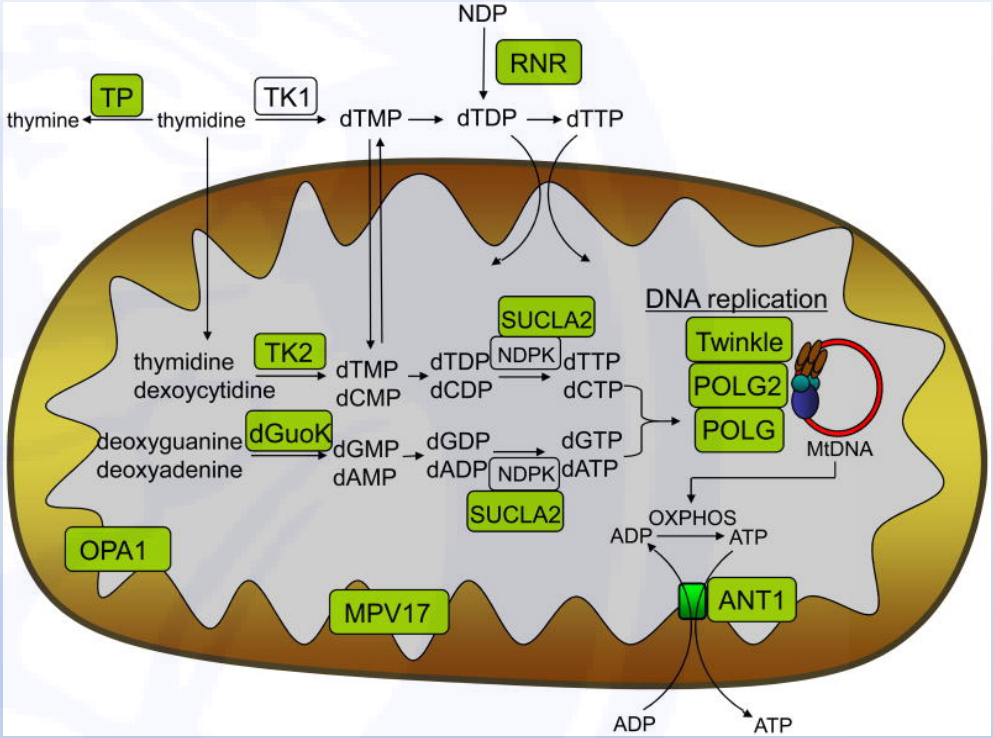


Axial T2-weighted images show cerebellar atrophy with prominent fissures and hyperintense lesions in left inferior olivary nucleus (arrow in A), cerebellar white matter (asterisks in B) and dorso-medial thalami (arrows in C)

Neuroradiol J. 2016 Feb; 29(1): 46–48.
Published online 2016 Jan 11

Mitochondrial DNA Depletion

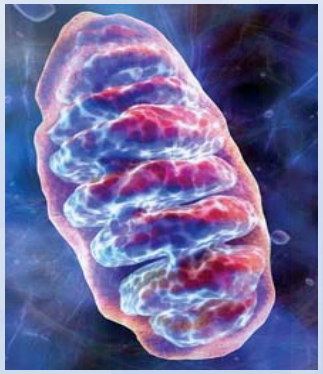
- Reduction on the mtDNA copy number without mutations and rearrangements
- Low mtDNA/nDNA ratio
- **Autosomal recessive inheritance** due to mutations in nuclear DNA

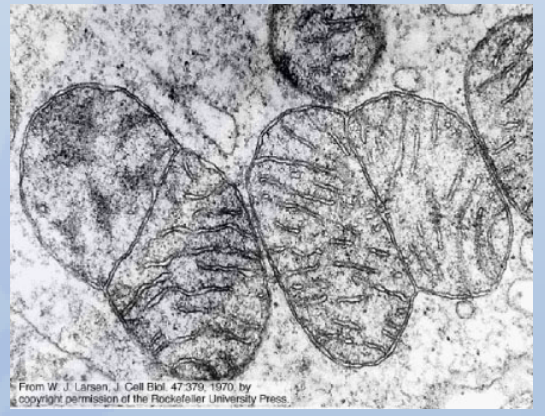


Chan SS, Copeland WC. *Biochim Biophys Acta 2009 May;1787(5):312-9.*

Controversies and misperceptions about mitochondrial disorders (MDs)

- They are rare
- Inherited from mothers
- **Can be diagnosed clinically**
- **Can be diagnosed on muscle biopsy**
- Untreatable
- Unpreventable





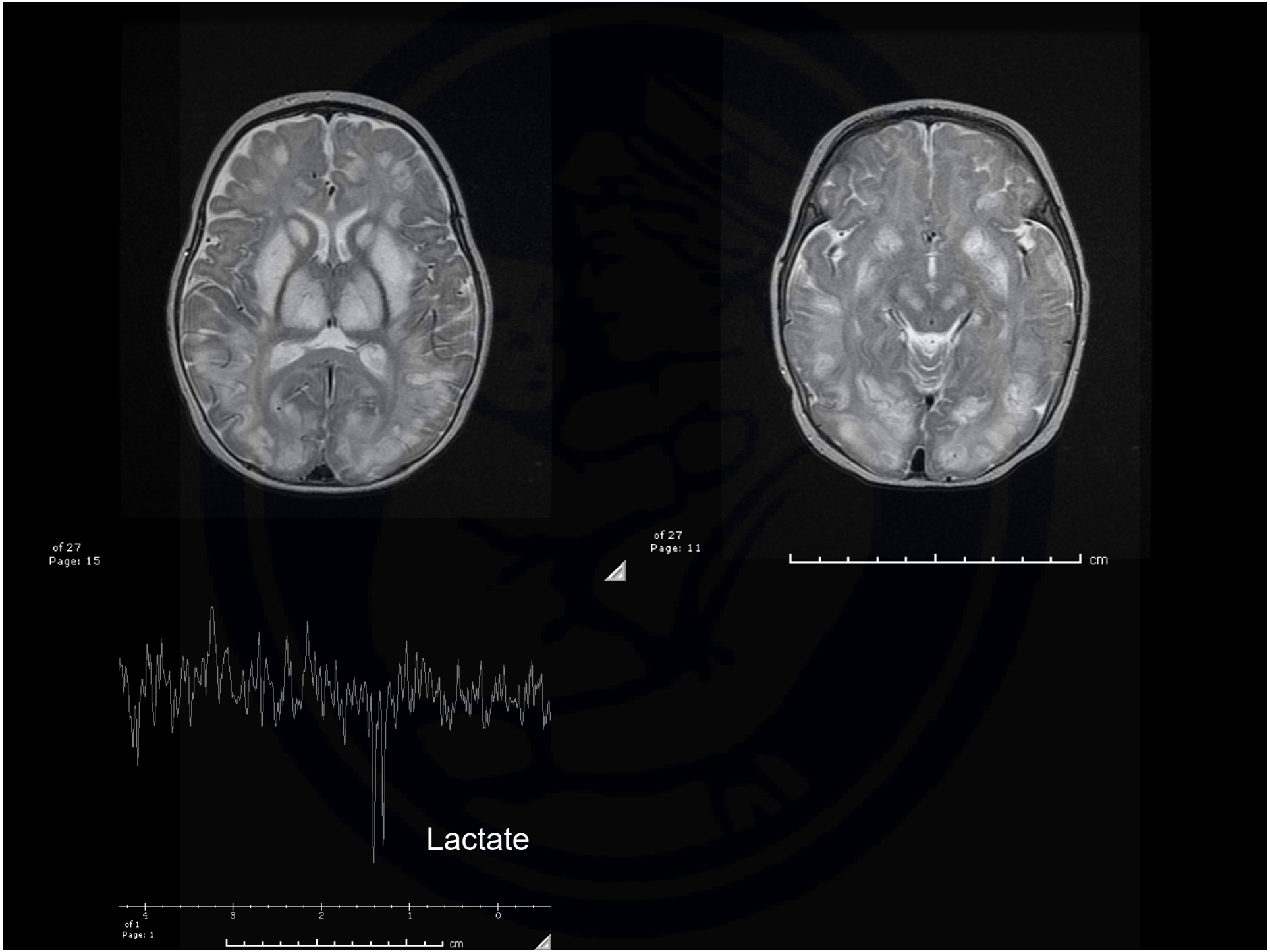
https://www.google.com/search?q=mitochondrial+division&biw

Slide 48

DS28 Suggest removing images if they are not necessary to convey informatino or illustrate a concept.
Dan Schwartz, 8/27/2020

Patient MR

- Female, uncomplicated pregnancy and delivery
- Irritable since birth
- At 3-½ months stopped feeding
- Admitted to Gen Peds service at BCH at 4 months
- Underwent head CT and brain MRI
- Highly elevated blood and CSFlactate


of 27
Page: 15
of 27
Page: 11
cm
Lactate
4
3
2
1
0
of 1
Page: 1
cm

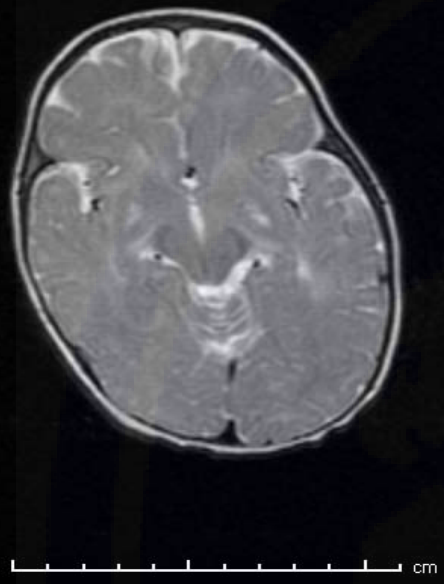
Patient MR

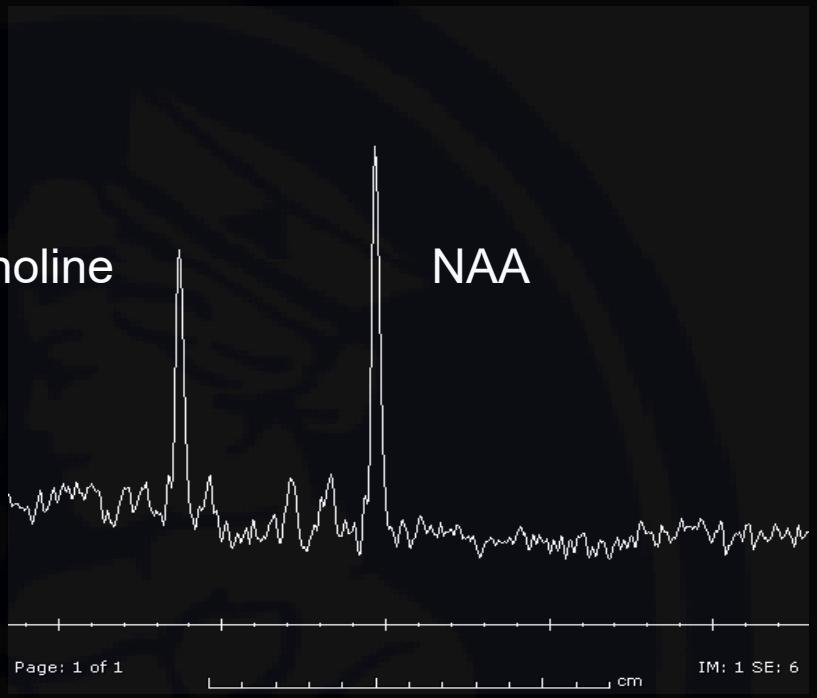
- WES homozygous D75N (c.223 G>A) variant in SLC19A3 gene
- Initially described in patients from Saudi Arabia as biotin-responsive basal ganglia disease (Ozand et al. 1998)
- New designation: thiamine metabolism dysfunction syndrome 2 (OMIM 607483)
- **THIAMINE METABOLISM DYSFUNCTION SYNDROME 2 (BIOTIN- OR THIAMINE-RESPONSIVE TYPE); THMD2**

Patient AR

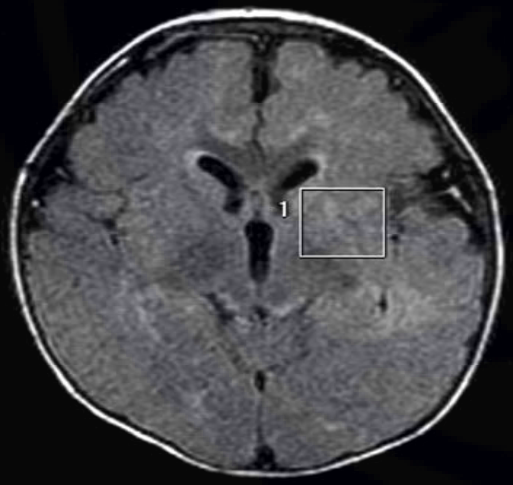
- 3-year-old boy
- Hypotonia since birth, global delay
- Elevated blood lactate
- Several ETC complex deficiencies on fresh muscle biopsy
- **DX: Mitochondrial disorder**

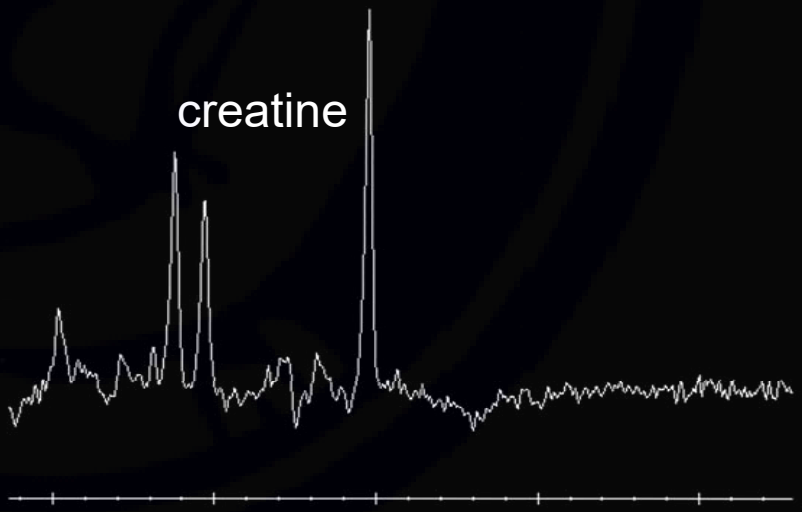
AR





SM





Patient AR

- Elevated urine creatine/creatinine ratio
- Large deletion in *SLC6A8*
- **Dx: X-linked Creatine transporter deficiency**
- Secondary OXPHOS defect with multiple complex deficiency

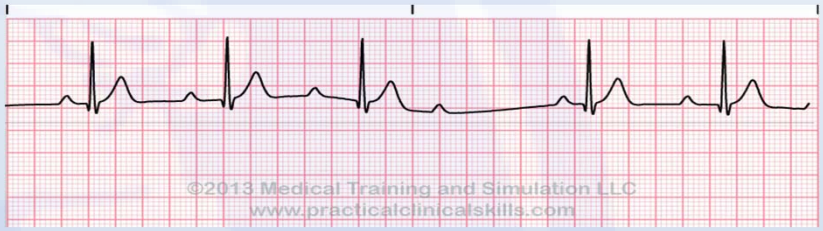
Slide 54

DS30 suggest generic body builder image if pic of Arnold isn't necesary.
THis image is in the public domain:
https://commons.wikimedia.org/wiki/File:US_Navy_070504-N-0995C-072_Chief_Mineman_Kevin_Sperling_appears_as_the_guest_body_b

Dan Schwartz, 8/27/2020

Who Should Be Referred for Evaluation?

- Developmental delay in a child with multi-organ involvement
- Cardiomyopathy with lactic acidosis
- Unexplained heart block

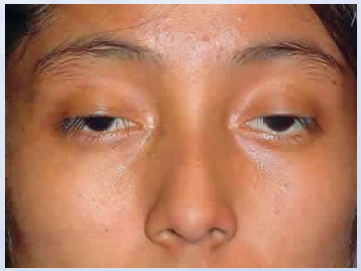


Slide 55

DS29 Suggest either enlarging image if it conveys important information or illustrates a concept, or remove if if's decorative.
Dan Schwartz, 8/27/2020

Who Should Be Referred for Evaluation?

- Developmental delay in a child with multi-organ involvement
- Cardiomyopathy with lactic acidosis
- Unexplained heart block
- Ophthalmoplegia, ptosis
- Severe GI dysmotility/pseudo-obstruction



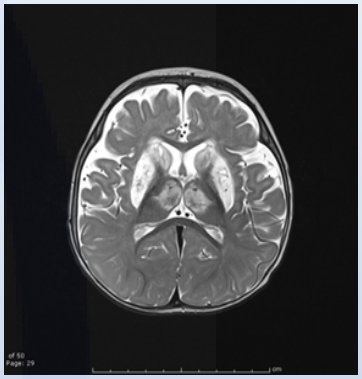
Slide 56

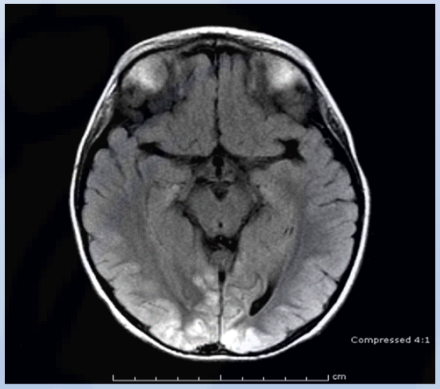
DS31 source info?

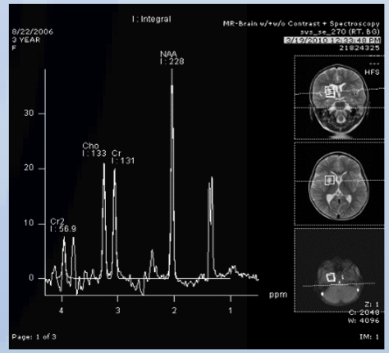
Dan Schwartz, 8/27/2020

Who Should Be Referred for Evaluation?

- Developmental delay in a child with multi-organ involvement
- Cardiomyopathy with lactic acidosis
- Unexplained heart block
- Ophthalmoplegia, ptosis
- Severe GI dysmotility/pseudo-obstruction
- Basal ganglia involvement consistent with Leigh disease
- Lactate peak on MRS
- Cerebral stroke-like lesions in a nonvascular distribution



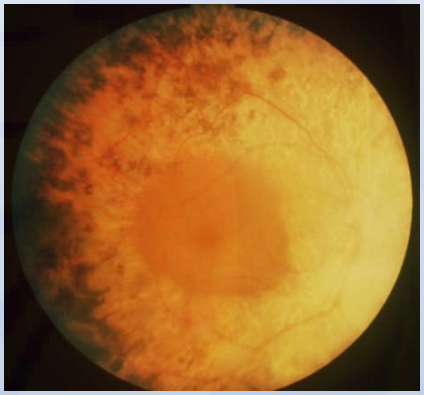




Who Should Be Referred for Evaluation? +/-

- Failure to thrive, short stature
- Poor stamina, exercise intolerance
- Hypotonia, ataxia, intractable seizures, unexplained movement disorder, neurosensory hearing loss
- Optic nerve hypoplasia, pigmentary retinopathy
- Renal tubular dysfunction
- Chronic or cyclic vomiting, chronic unexplained constipation or diarrhea
- https://www.google.com/search?q=child+vomiting&biw

Retinitis Pigmentosa

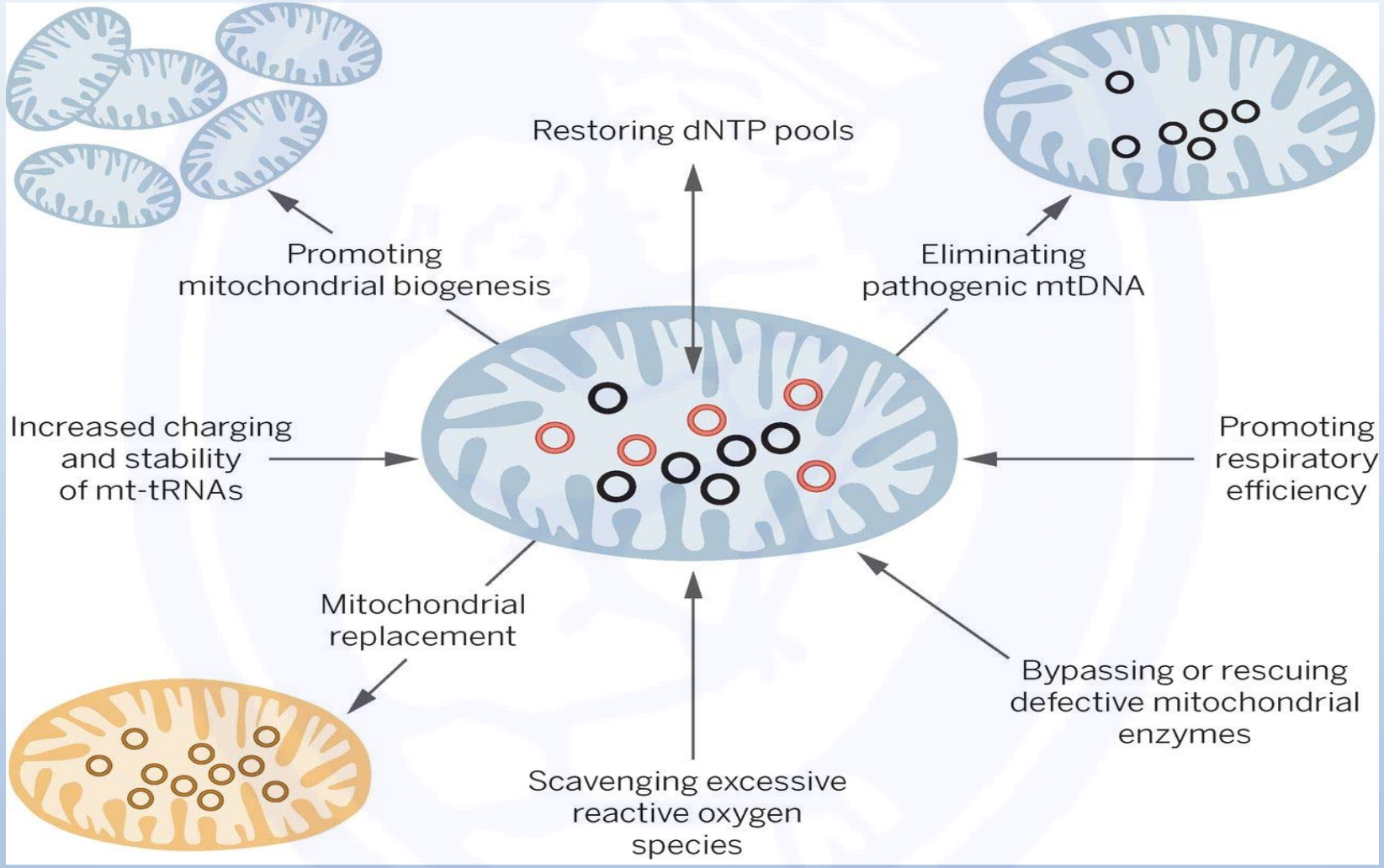


Slide 58

DS32 source info?

Dan Schwartz, 8/27/2020

Therapy of Mitochondrial disorders



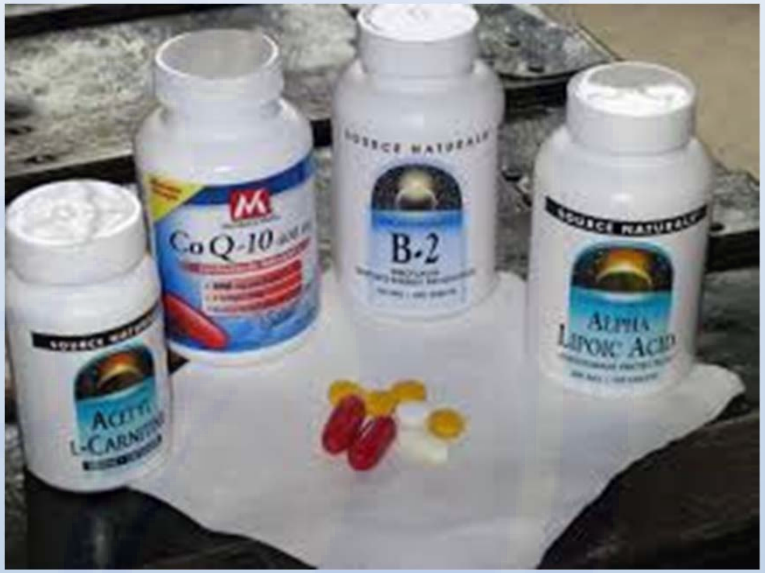
Lightowlers et al, Science, VOL 349 ISSUE 6255, 2015

Management

- **Medical management of symptoms**
  - e.g., seizures, spasticity, diabetes
- **Preventative measures**
  - e.g., avoiding illness, avoiding fasting, etc.
- **Supportive services**
  - PT, OT, vision therapy, hearing aids, augmented communication
- **Diet**
  - Pyruvate dehydrogenase deficiency: low-carb, high-fat diet
  - Most: balanced diet

"Mito Cocktail"

- Coenzyme Q10 (Ubiquinone)
- Ubiquinol
- Creatine
- Carnitine
- Thiamine
- Riboflavin
- Lipoic acid
- Vitamin C
- Vitamin E
- N-Acetyl cysteine (NAC)



Patient care standards for primary mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society

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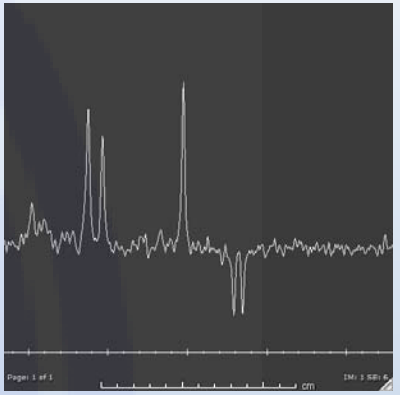
The purpose of this statement is to provide consensus-based recommendations for optimal management and care for patients with primary mitochondrial disease. This statement is intended for physicians who are engaged in the diagnosis and management of these patients. Working group members were appointed by the Mitochondrial Medicine Society. The panel included members with several different areas of expertise. The panel members utilized surveys and the Delphi method to reach consensus. We anticipate that this statement will need to be updated as the field continues to evolve. Consensus-based recommendations are provided for the routine care and management of patients with primary genetic mitochondrial disease.

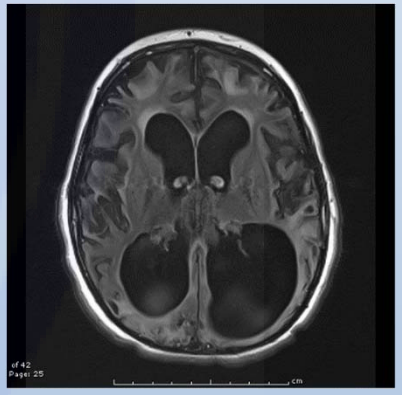
Genet Med advance online publication 27 July 2017

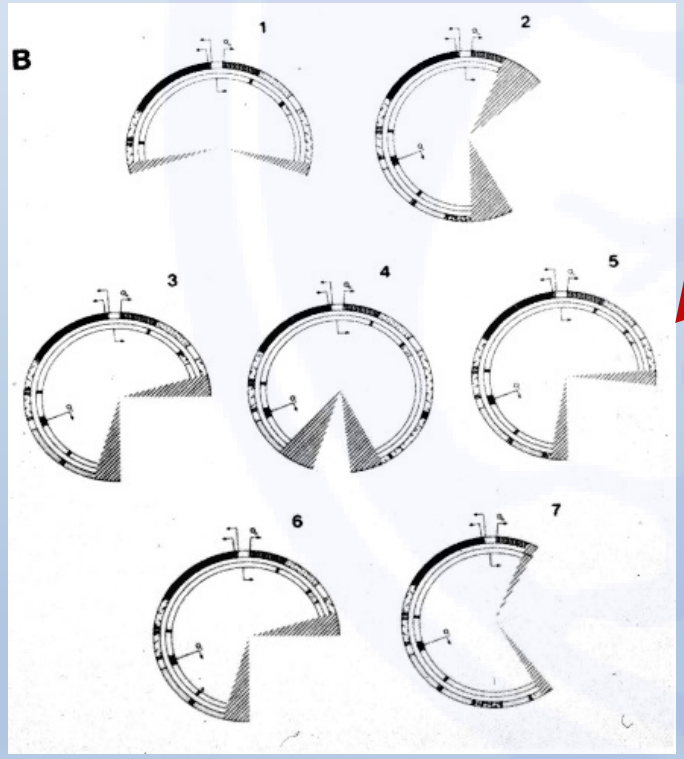
Key Words: care guidelines; consensus criteria; Delphi method; mitochondrial disease; treatment

Specific Therapies

- DCA (dichloroacetate) for lactic acidosis
- L-arginine for MELAS, potentially Citrulline
- Folinic acid for KSS, POLG and other MDs



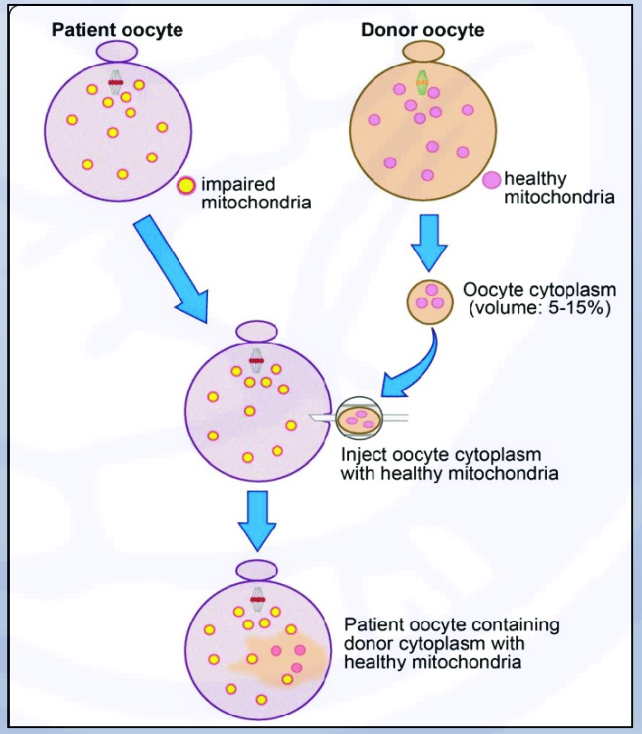




Zeviani M et al. Neurology 1998;51(6)

Mitochondrial replacement therapy

Mitochondrial replacement therapy



Schatten H et al. Endocrinology 2014;12(1):111

Slide 64

DS34 Suggest removing 3 parent baby image b/c it repeats slide title, and enlarge otehr two images
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Summary

- Heterogeneous group of disorders
- Mitochondrial diseases (MDs) are not rare
- Important to recognize, but Difficult to diagnose
- Suspected MDs should be referred for evaluation
- Genetic testing should be attempted on every patient with suspected mitochondrial disorder

http://alumnus.caltech.edu/~kantner/zebras/pictures.html