Mitochondrial disease genetics

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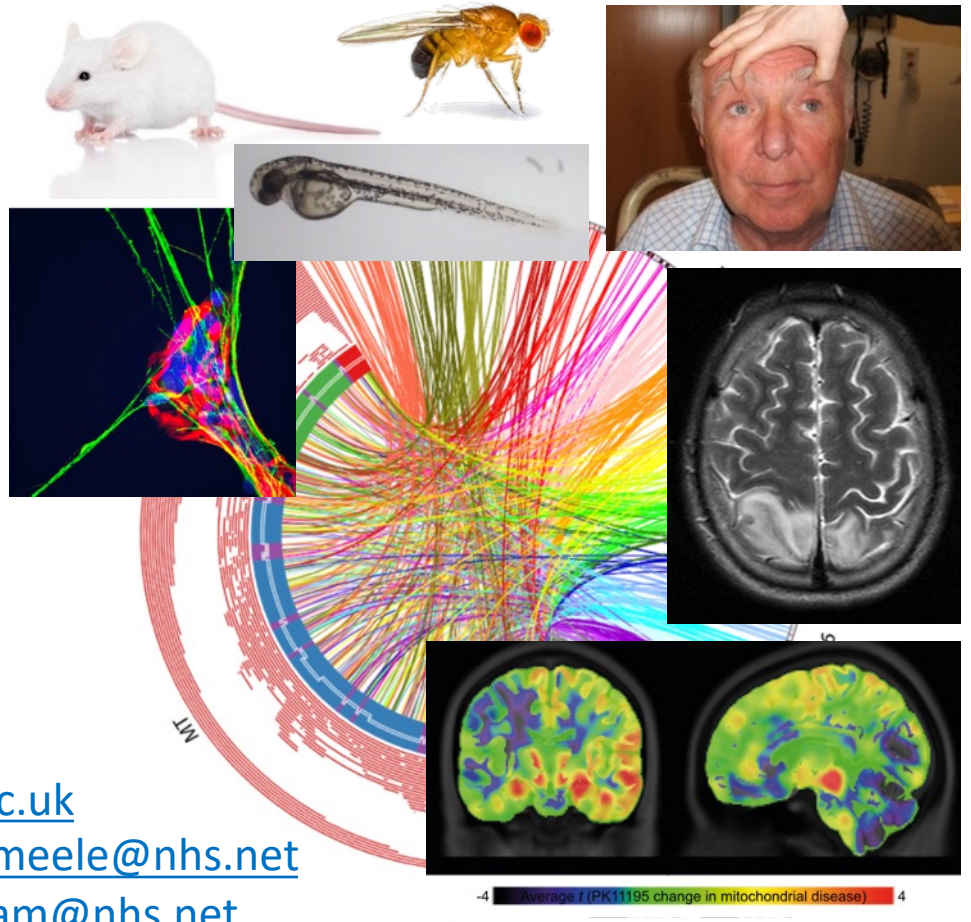
MITO CAMB

Cambridge Clinical Mitochondrial Research Group



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Outline

Case 1/2: Stroke-like episodes

- What are mitochondria
- Oxidative phosphorylation
- Inheritance of primary mitochondrial disease
- Mitochondrial disease overview and classical syndromes
- The mitochondrial genome (1)

Case 3: CPEO

- The mitochondrial genome (2): heteroplasmy

Case 4: Nuclear or mitochondrial?

- mtDNA maintenance disorders
- A few more classical syndromes

Case 1

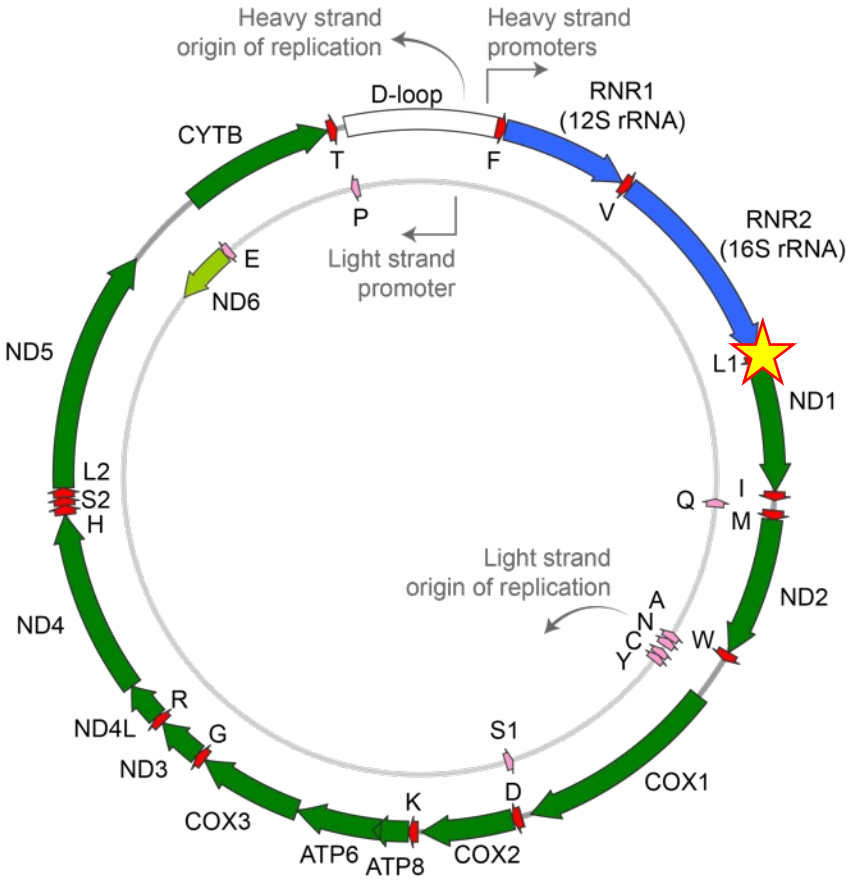
MELAS: Mitochondrial encephalomyopathy with lactic acidosis and *stroke-like episodes*

Typical (diagnostic) features:

- Stroke-like episodes <40y
- Seizures and/or dementia
- Ragged-red fibres (muscle biopsy), lactic acidosis

+ many additional features: Diabetes mellitus, cardiomyopathy, hearing loss, pigmentary retinopathy, ataxia,…

Most frequently due to m.3243A>G mutation in the mitochondrial DNA (leucine tRNA, MT-TL1)



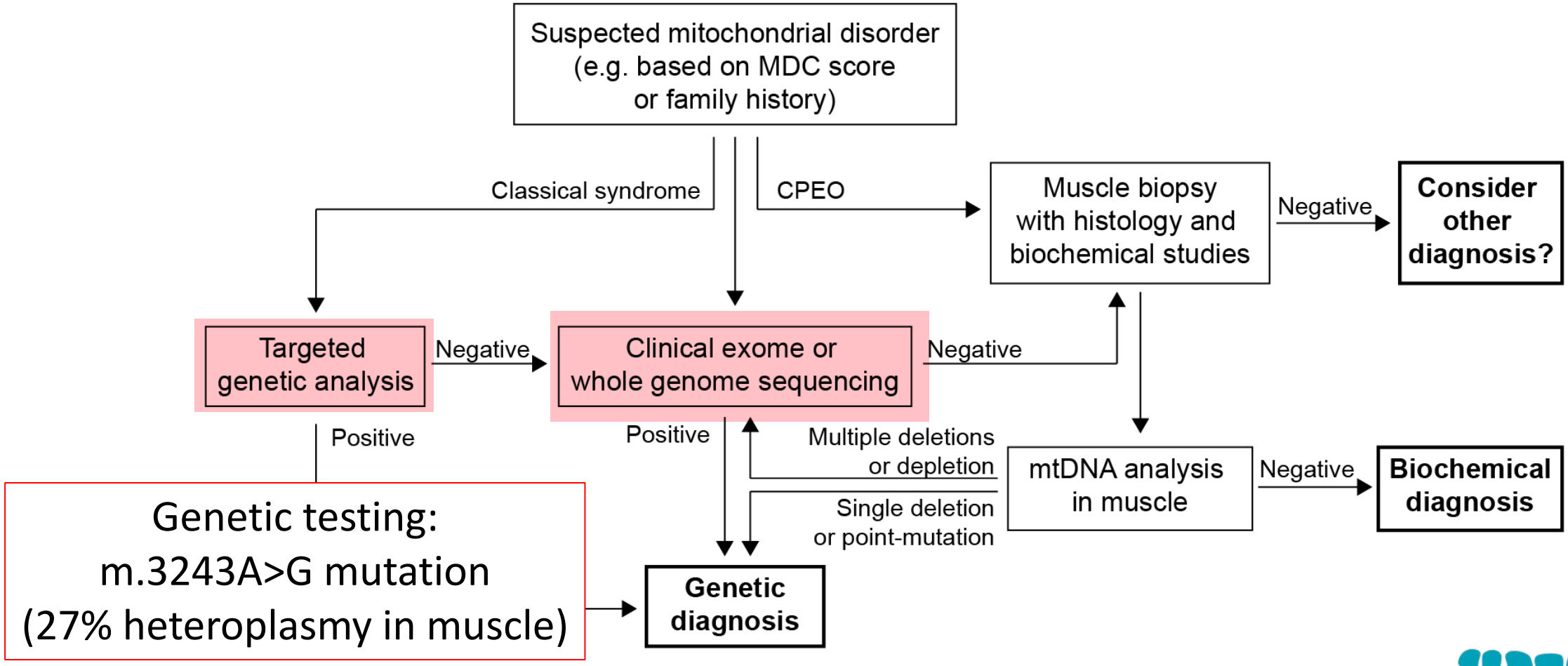
van den Ameele et al., Semin Cell Dev Biol, 2019.

Trends in Genetics
CellPress REVIEWS
Review

Mitochondrial Diseases: A Diagnostic Revolution

Katherine R. Schon,[1,2] Thiloka Ratnaike,[1,2,3] Jelle van den Ameele,[1,2] Rita Horvath,[1] and Patrick F. Chinnery[1,2,*]

Approach to a patient with suspected mitochondrial disease



van den Ameele et al., in Emergencies in Neuromuscular Disorders, 2022; Schon et al., Trends in Genetics, 2021.

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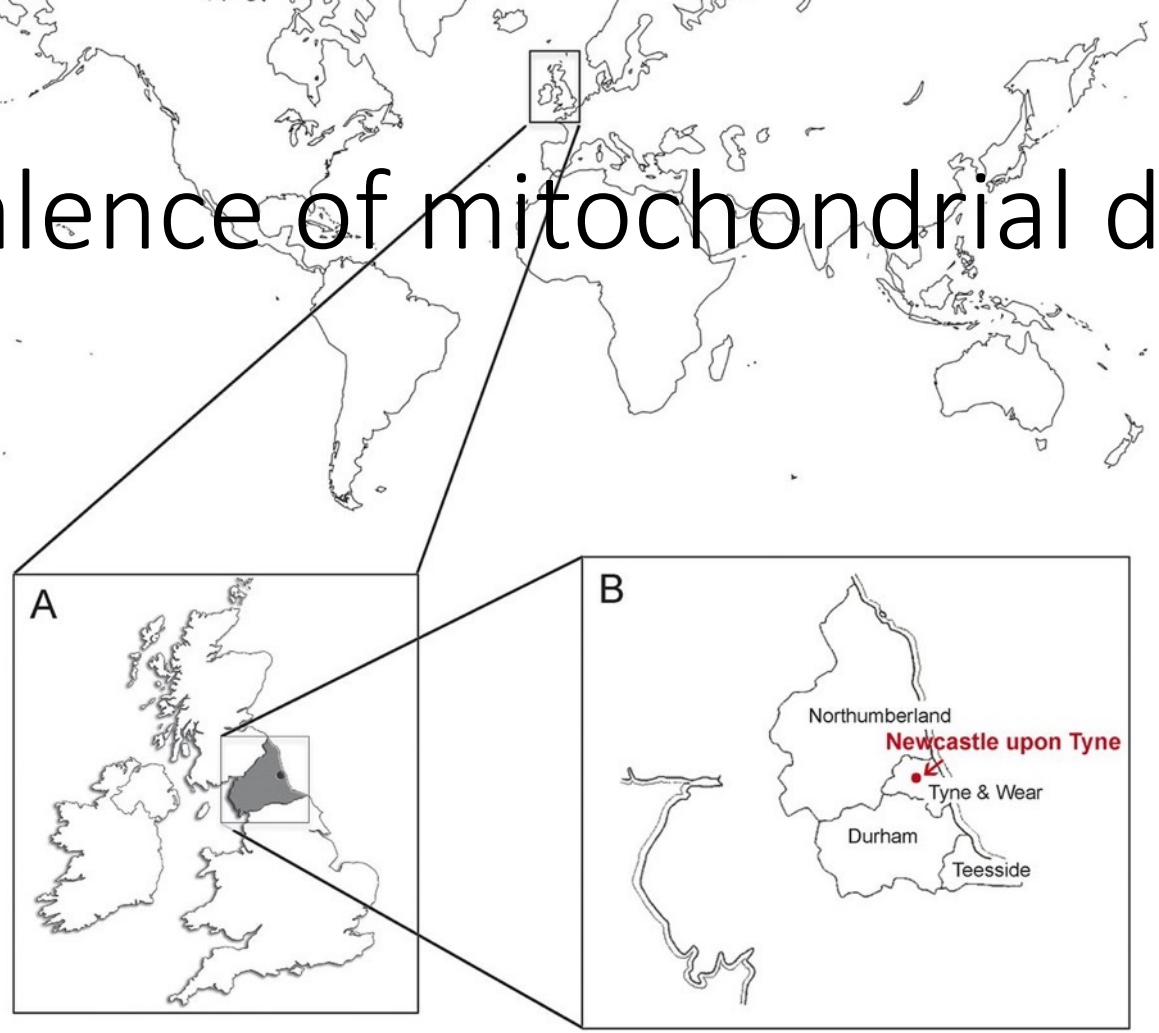
Case 2: Stroke-like episodes

Prevalence of mitochondrial disease

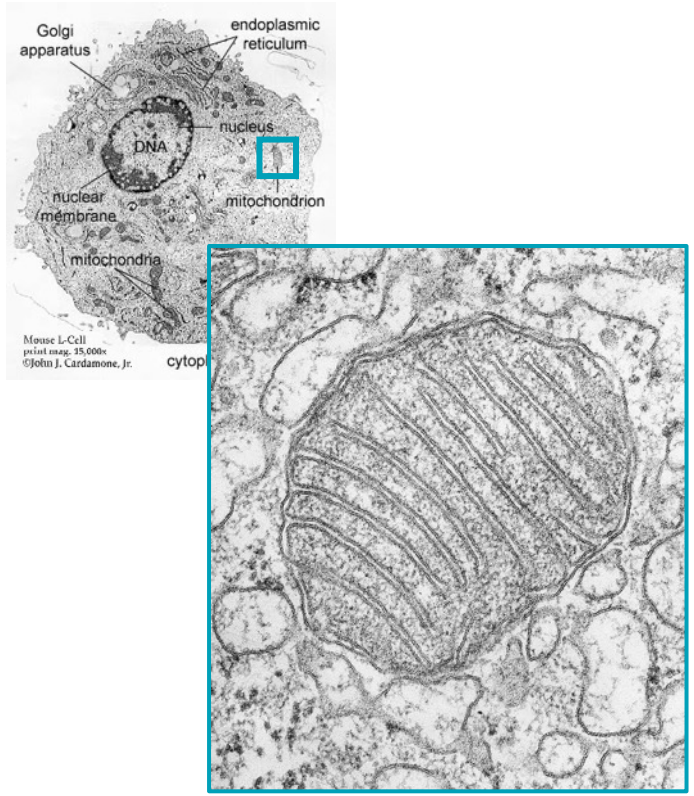


~1/5,000 adults affected by mitochondrial disease

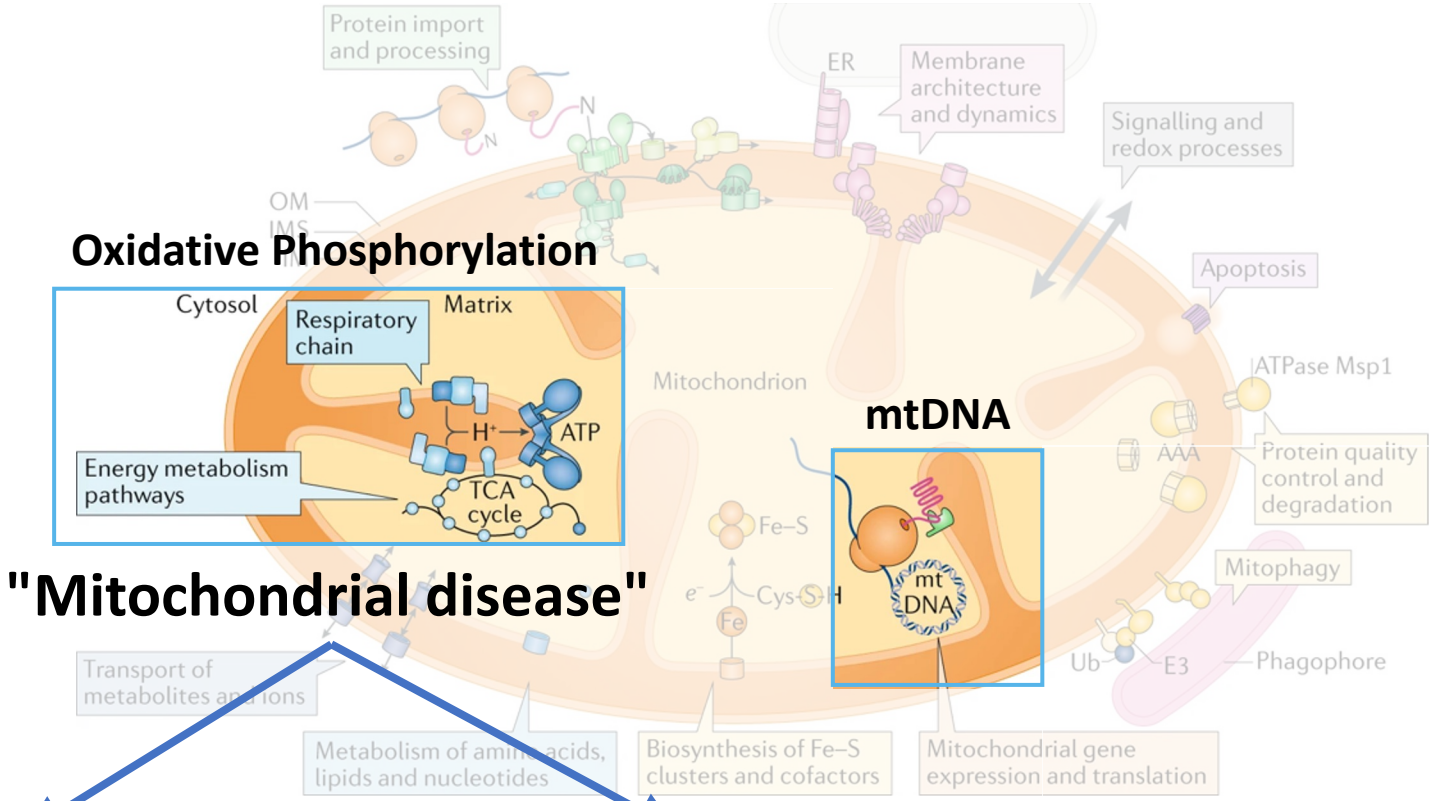
Most frequent type of inherited neurological disease,
but many different genes and often complex clinical presentation

Schaefer et al., Ann Neurol, 2008; Gorman et al., Ann Neurol, 2015.

Mitochondria



Mitochondria



"Mitochondrial disease"

Primary (genetic) mitochondrial disease

Mitochondrial contribution to common disease

Pfanner et al., Nat Rev Mol Cell Biol, 2019

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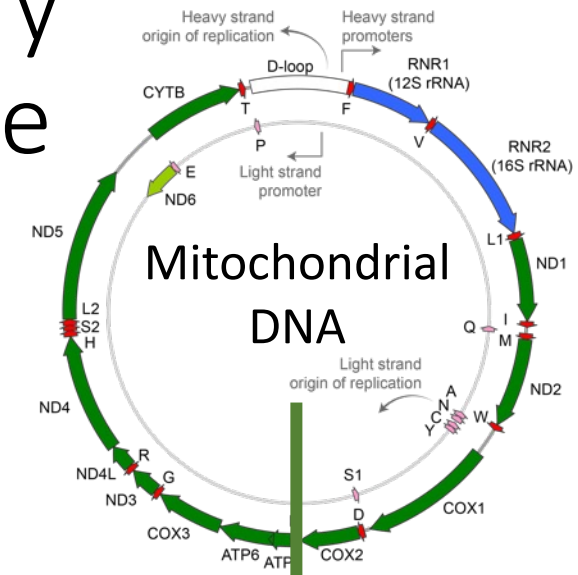
Inheritance of primary mitochondrial disease

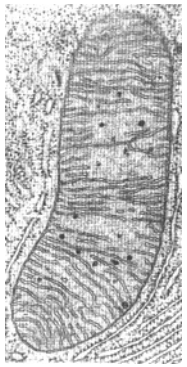
Nuclear DNA (chromosomes)

Mitochondrial DNA maintenance

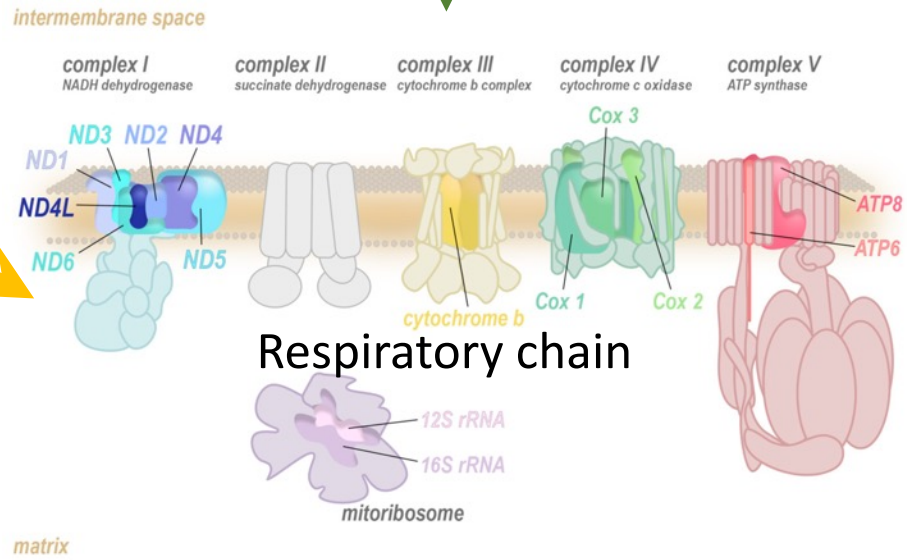
e.g. POLG, Twinkle, TYMP, RRM2B,…

Respiratory chain function and assembly

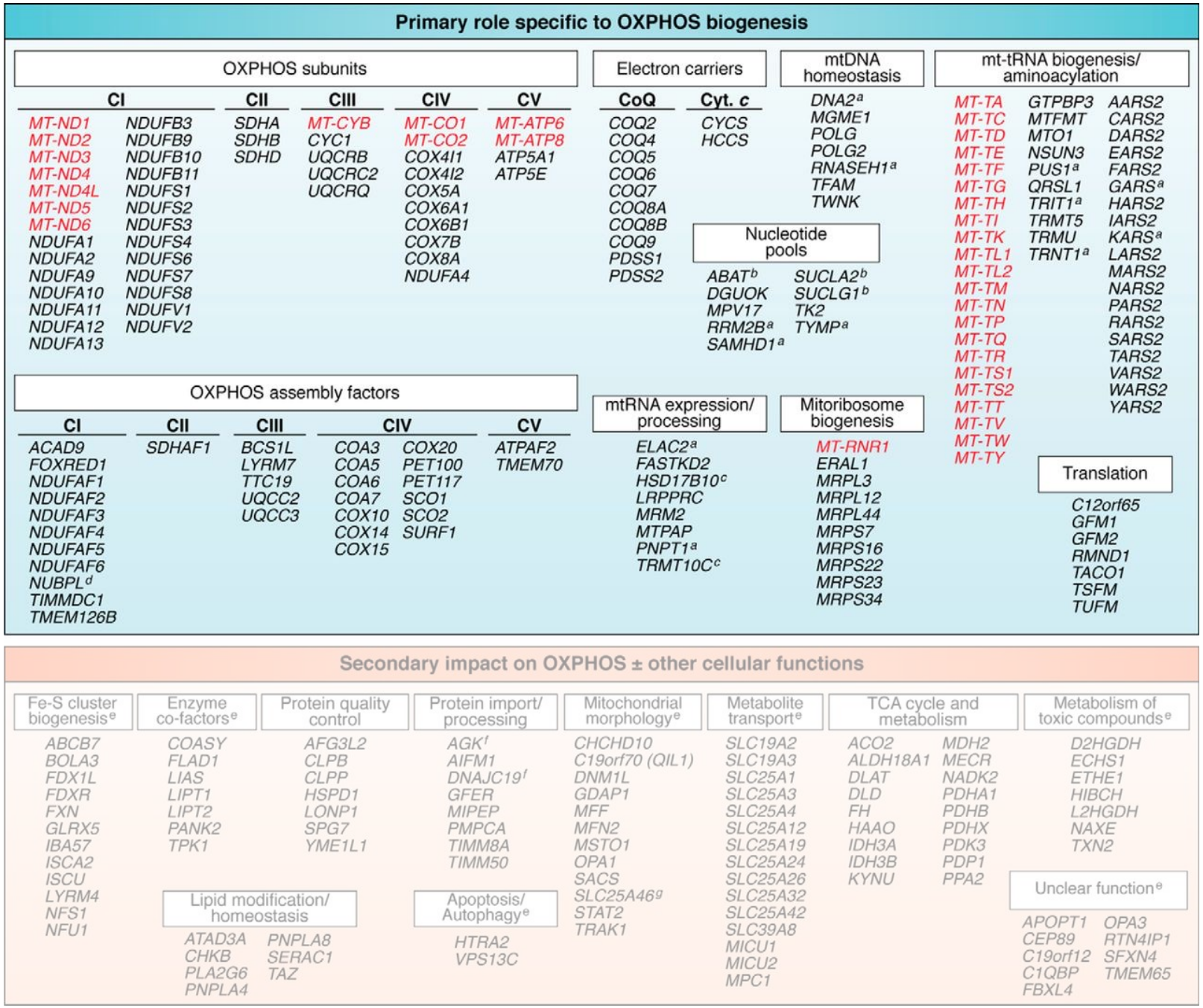




OxPhos Complexes I, III, IV, V (not II)



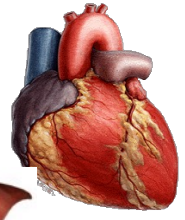
Respiratory chain

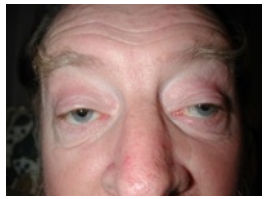


Frazier et al., J Biol Chem, 2017

Clinical features of mitochondrial disorders

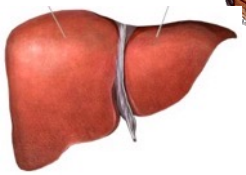
Cardiomyopathy

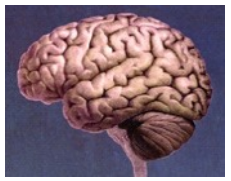




Ophthalmoplegia / ptosis

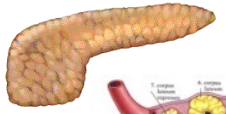
Liver Failure



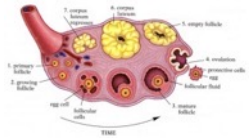


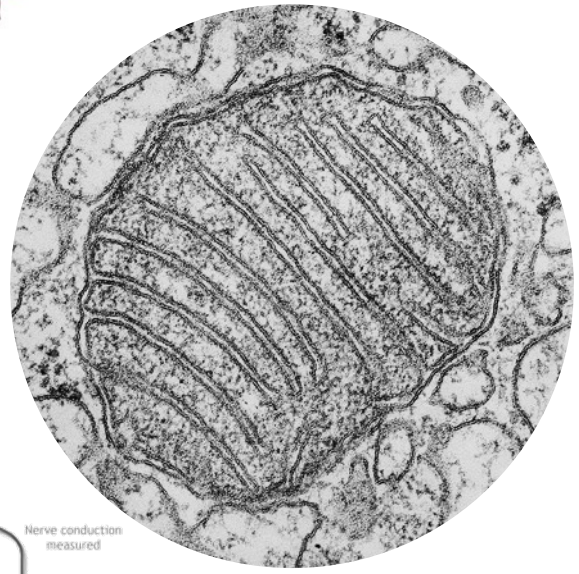
Encephalopathy
Epilepsy / dementia
Migraine

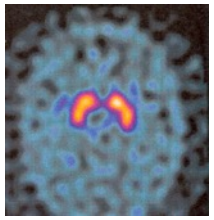
Diabetes



Gonadal failure

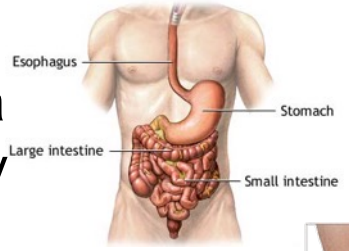


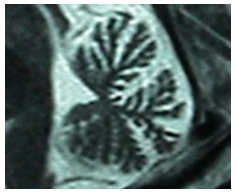




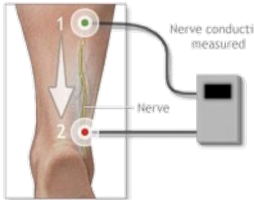
Parkinsonism

Dysphagia
Dysmotility





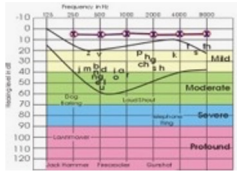
Ataxia



Axonal
sensori-motor
neuropathy

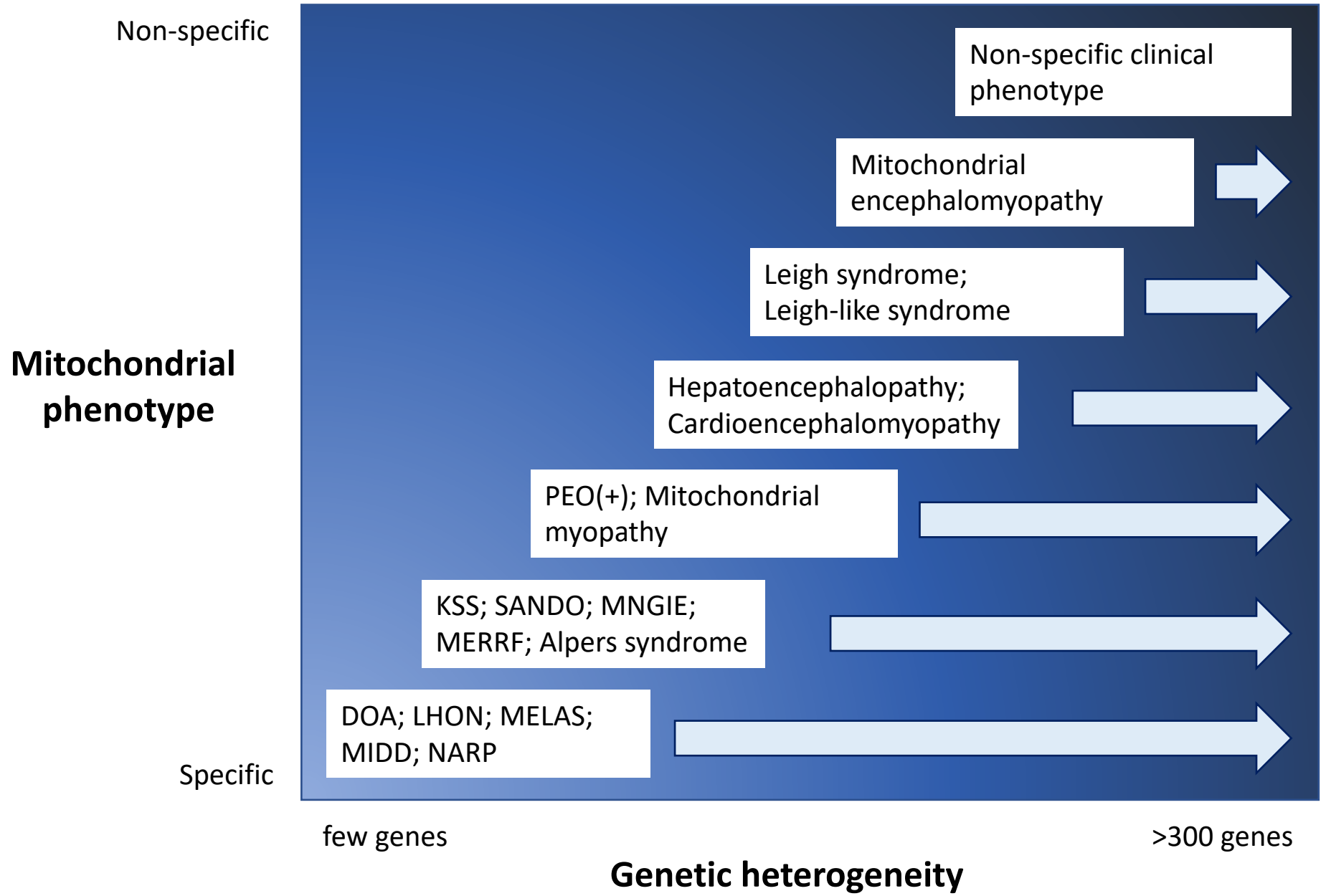
Migraine

Myopathy



Deafness

(Slide from Patrick Chinnery)



(Slide from Rita Horvath)

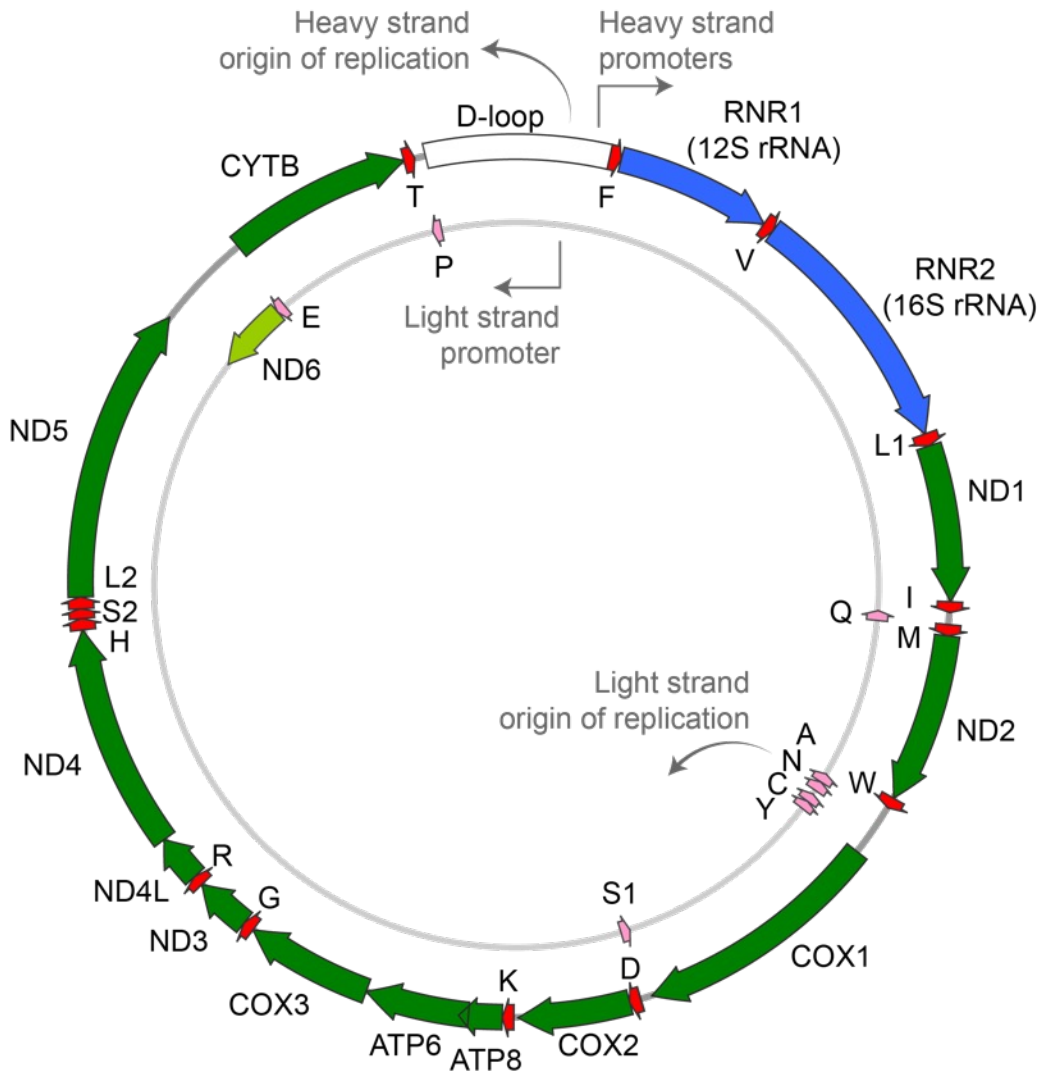
Classical syndromes

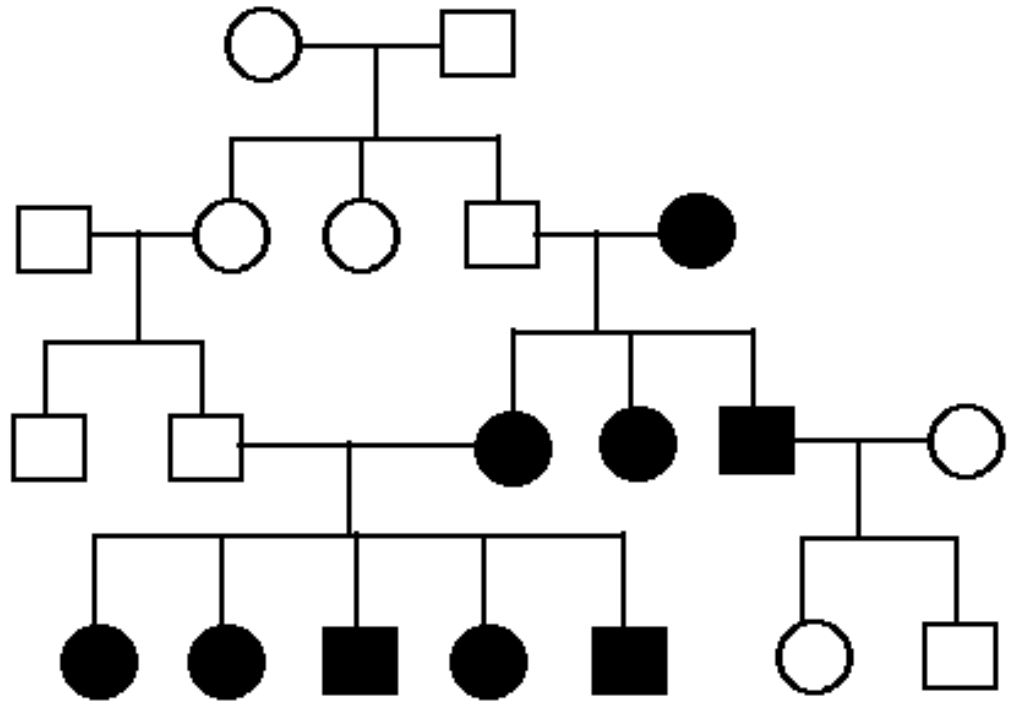
- Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)
- Leber's hereditary optic neuropathy (LHON)
- Chronic progressive external ophthalmoplegia (CPEO)
- Kearns-Sayre Syndrome
- Pearson Syndrome
- Leigh Syndrome
- Mitochondrial inherited diabetes and deafness (MIDD)
- Myoclonic epilepsy with ragged red fibers (MERRF)
- Neuropathy, ataxia, retinitis pigmentosa (NARP)
- Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)

The mitochondrial genome (1)

- Circular genome
- Contributes to OxPhos and mitochondrial translation
- Under control of nuclear genome
- Maternal inheritance

- Many copies in each cell



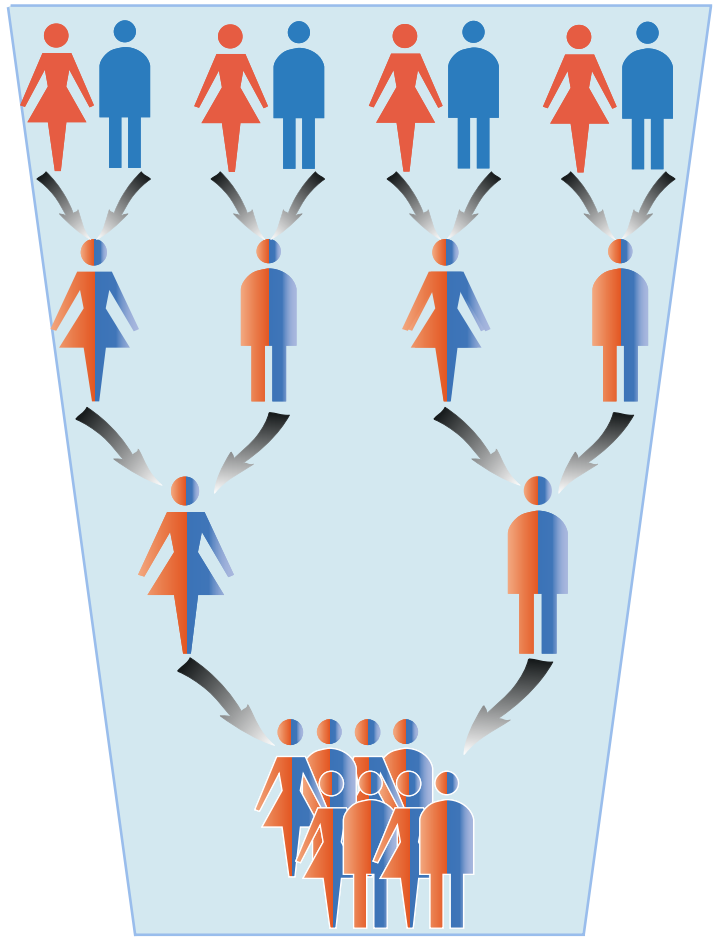


Characteristics of Mitochondrial Inheritance

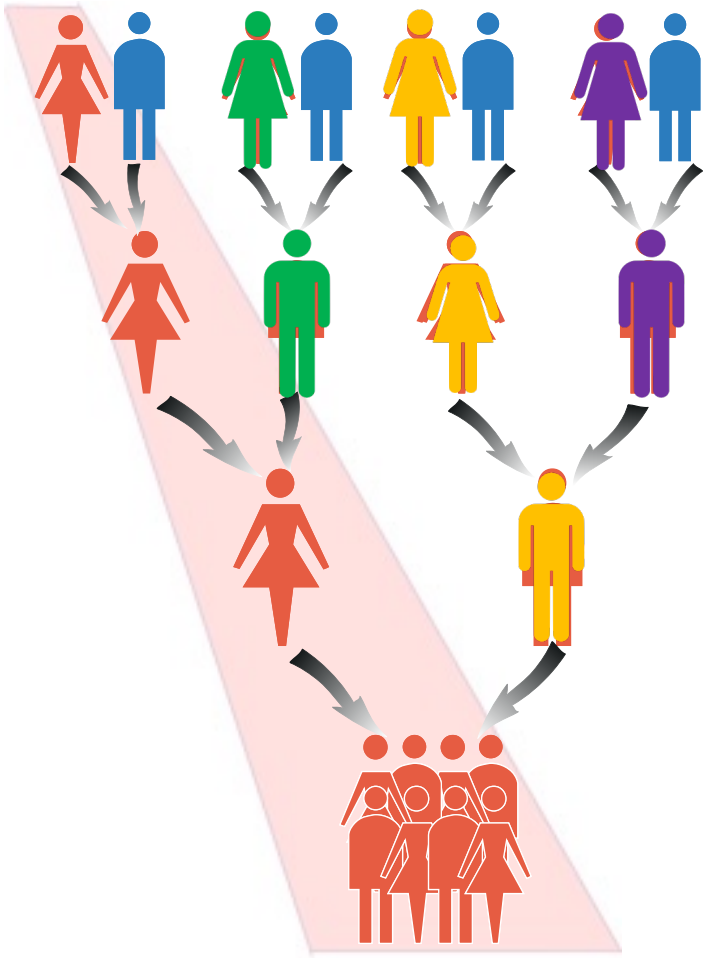
- Mitochondria are inherited from the mother.
- All offspring of an affected or carrier female are at risk of being affected.
- All daughters of an affected or carrier female are at risk of transmitting the condition.
- Affected males cannot pass the condition to any of their children.

Maternal inheritance of mtDNA

Nuclear DNA inherited from both mother and father



Mitochondrial DNA inherited only from mother



(Slide from Patrick Chinnery)

Casus 3

Klinische diagnose: Kearns-Sayre Syndrome

Frequent klinisch beeld bij een patient met een single mtDNA deletion:

1. Retinitis pigmentosa
2. CPEO
3. Hartritme stoornissen

(4. begin <20 jaar)

Vaak met:
Ataxie, verstandelijke beperking of dementie, doofheid, Myopathie, Gastro-intestinale problemen, …

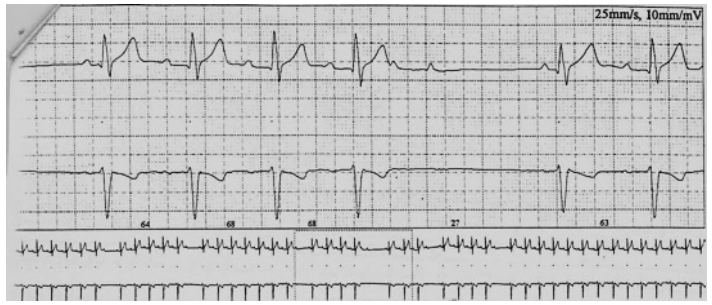
Klinisch beeld vaak gecorreleerd met grootte van de mtDNA deletie en heteroplasmy level.

Retinitis Pigmentosa, External Ophthalmoplegia, and Complete Heart Block

Unusual Syndrome with Histologic Study in One of Two Cases

THOMAS P. KEARNS, M.D., and GEORGE P. SAYRE, M.D., Rochester, Minn.

Wikipedia

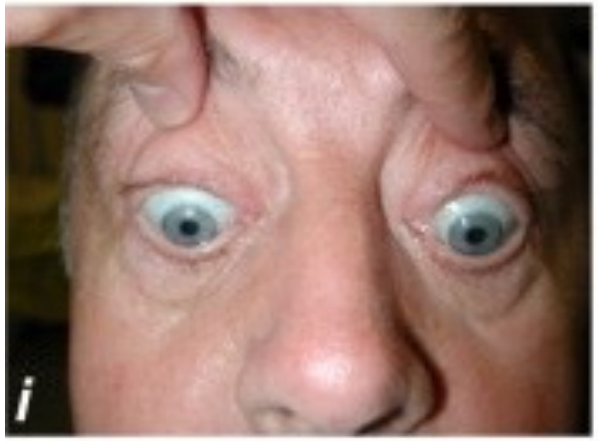


AMA Arch Ophthalm, 1958

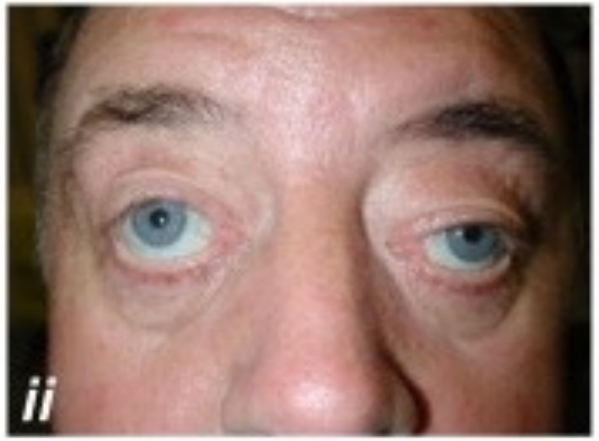
Fig. 1 (Case 1).—Patient with retinitis pigmentosa, external ophthalmoplegia, and atrioventricular heart block.

Chronic progressive external ophthalmoplegia (CPEO)

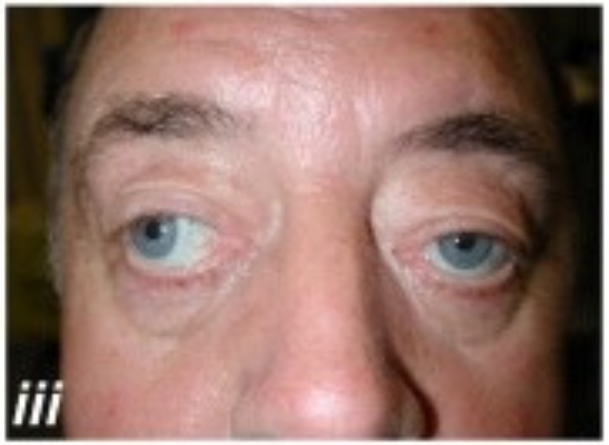
Down



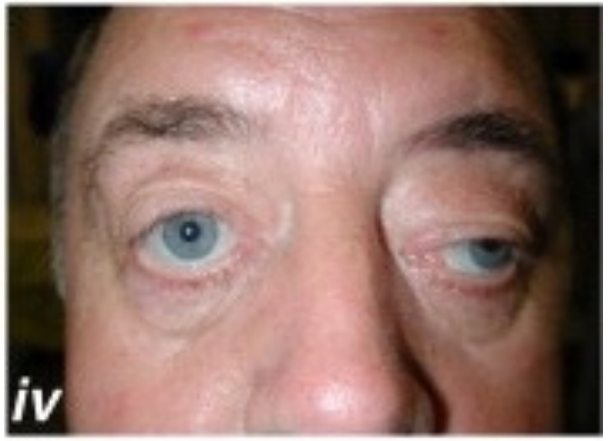
Up



Right



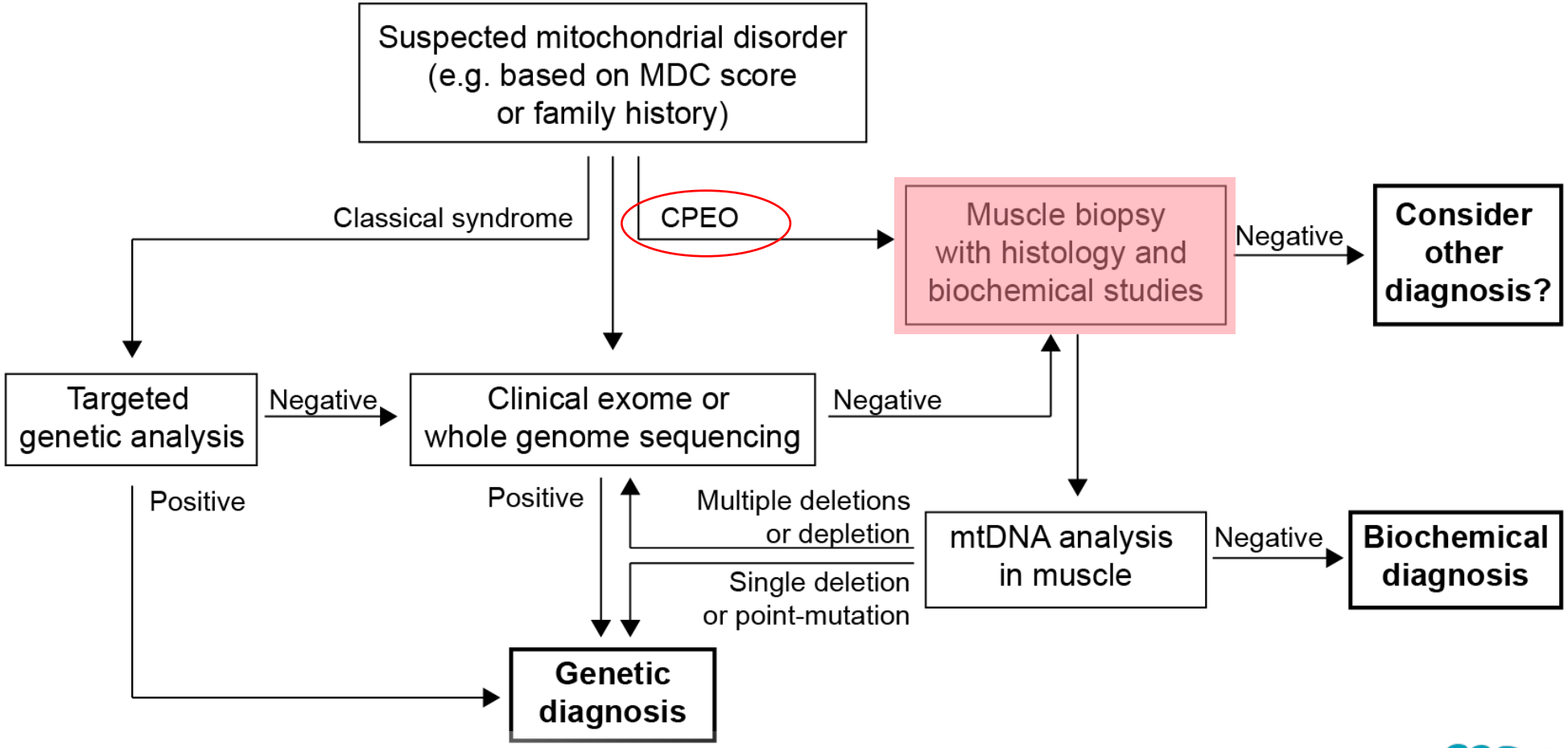
Left



+ ptosis (droopy eyelids)

Gorman and Taylor, Saudi J Opht, 2011.

Approach to a patient with suspected mitochondrial disease



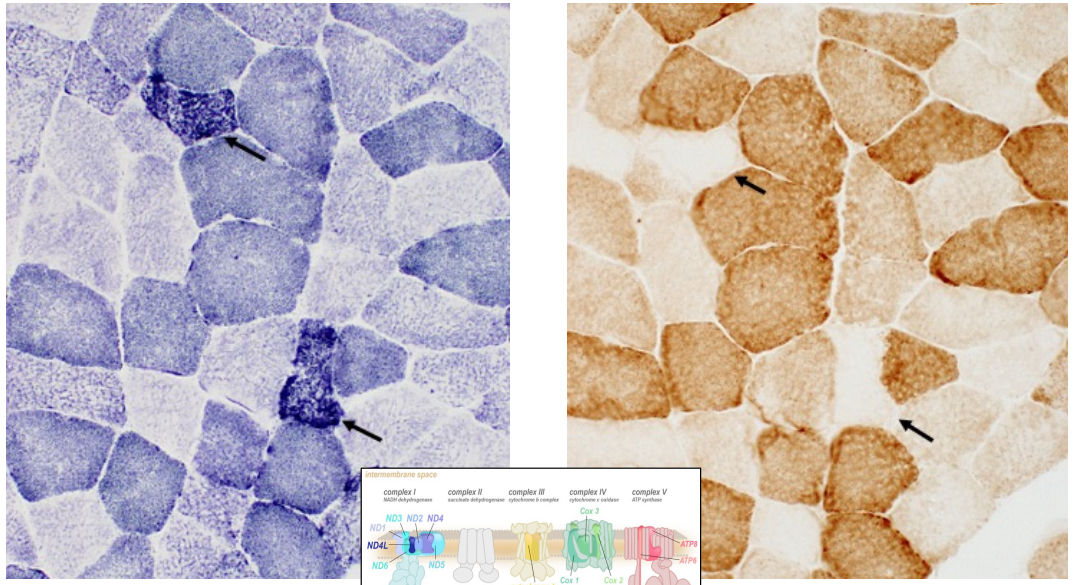
van den Ameele et al., in Emergencies in Neuromuscular Disorders, 2022; Schon et al., Trends in Genetics, 2021.

Case 3: mtDNA heteroplasmie
(of: waarom nog steeds een spierbiopsie?)

Example COX-SDH staining
(patient data removed for sharing)

Combined COX-SDH x200

neuromuscular.wustl.edu



SDH (complex II):
Completely nuclear encoded

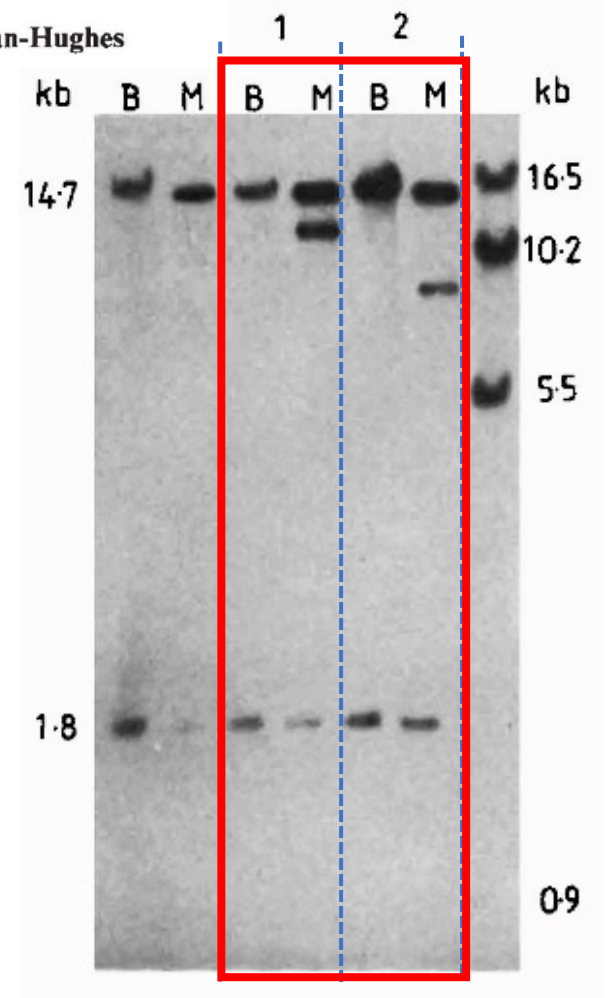
COX (complex IV):
In part mitochondrial encoded

Thanks to Rob Taylor, Newcastle

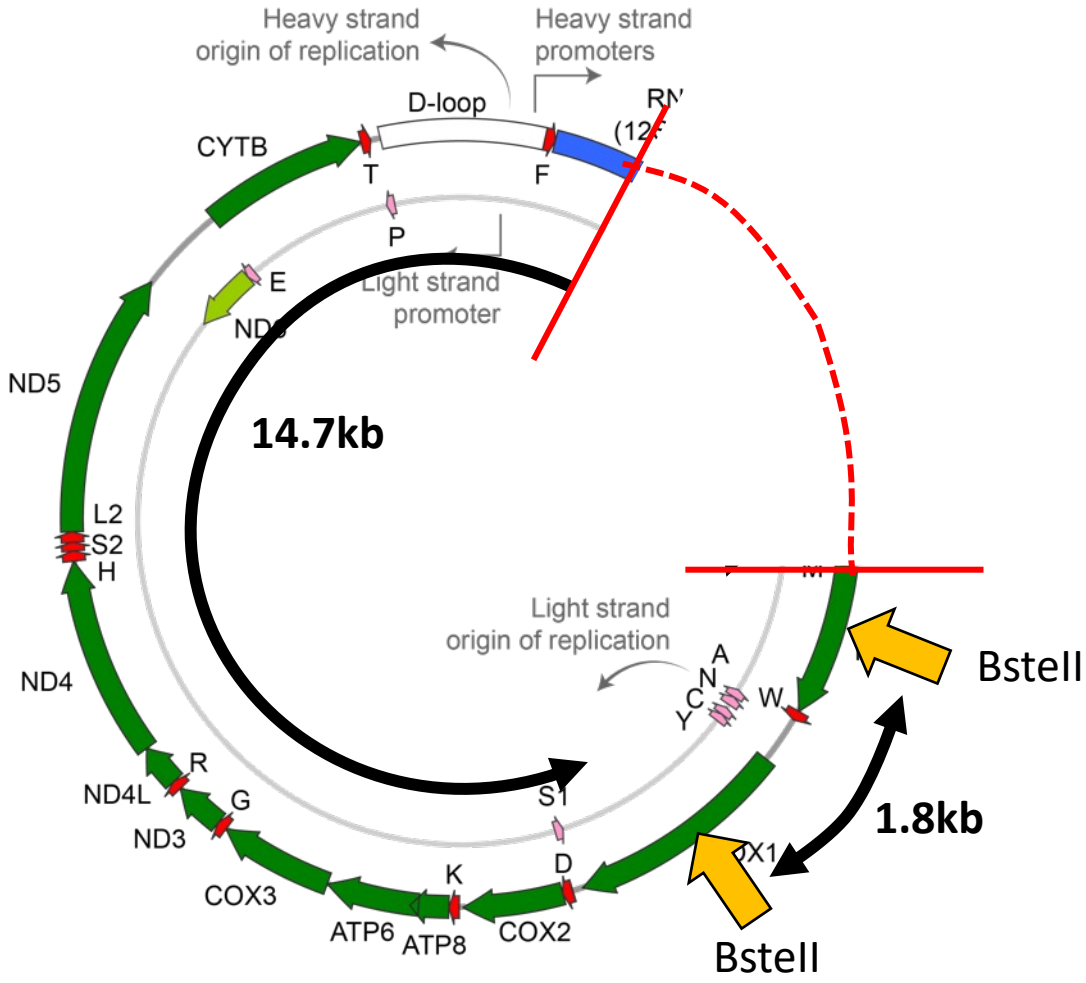
mtDNA heteroplasmie
(of: waarom nog steeds een spierbiopsie?)

Deletions of muscle mitochondrial DNA in patients with mitochondrial myopathies

I. J. Holt, A. E. Harding & J. A. Morgan-Hughes



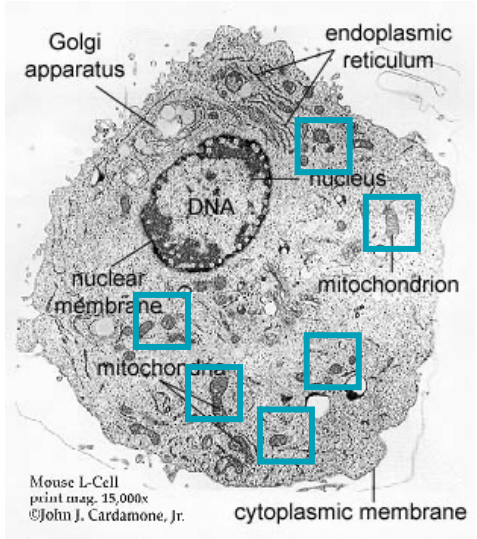
Holt et al., Nature, 1988



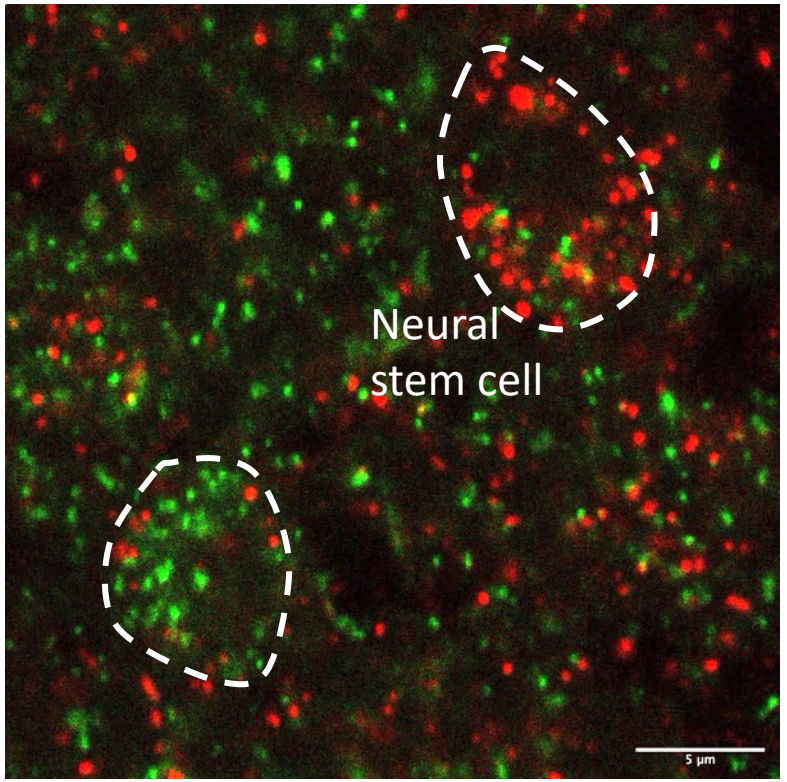
The mitochondrial genome (2)

- Circular genome
- Contributes to OxPhos and mitochondrial translation
- Under control of nuclear genome
- Maternal inheritance

- Many copies in each cell
  - Heteroplasmy vs homoplasmy
  - Heterogeneity in space and time
  - Genetic bottleneck

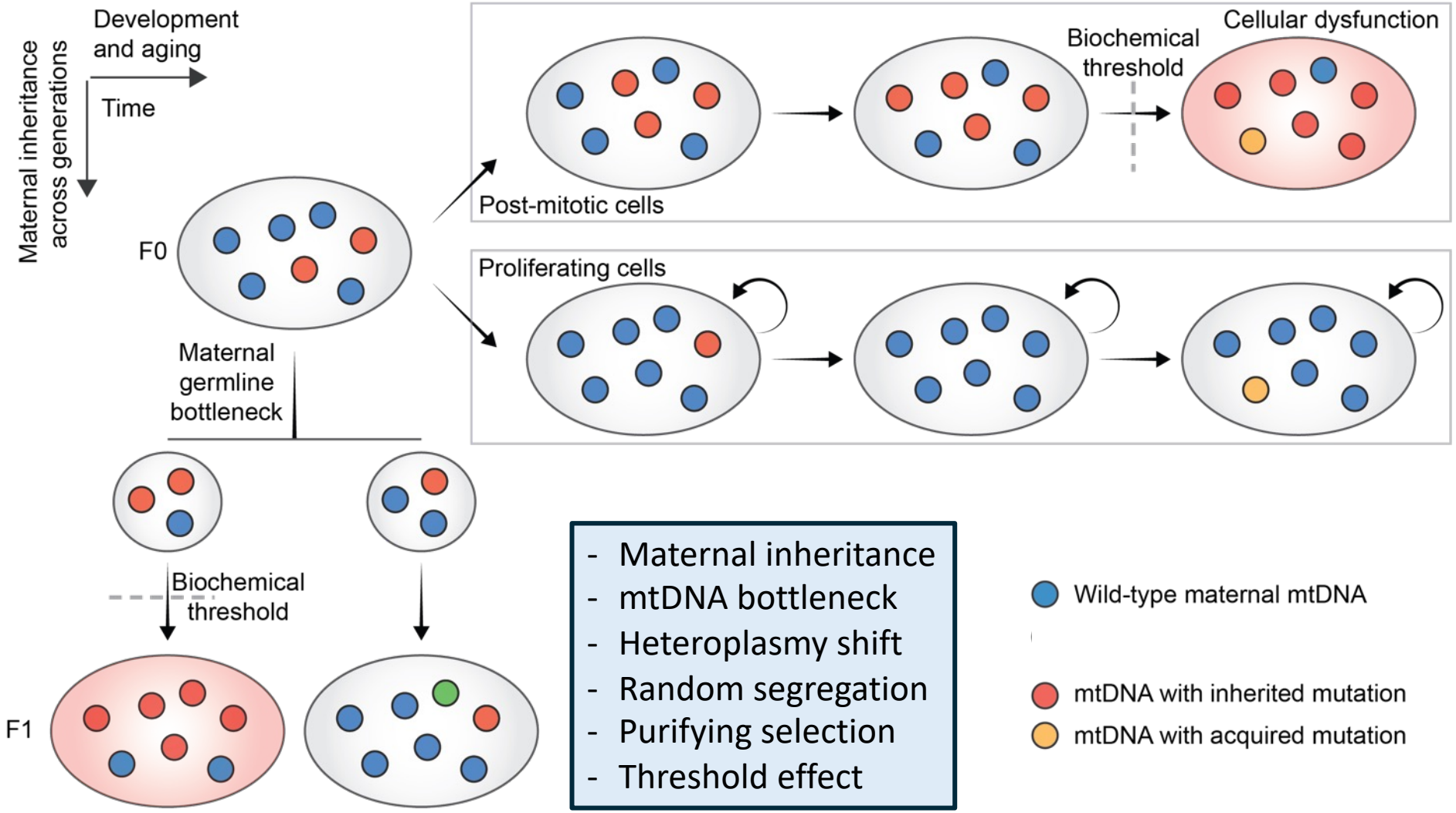


Brain of a heteroplasmic Drosophila strain



smFISH for wild-type mtDNA
smFISH for mutant mtDNA

mtDNA heteroplasmy

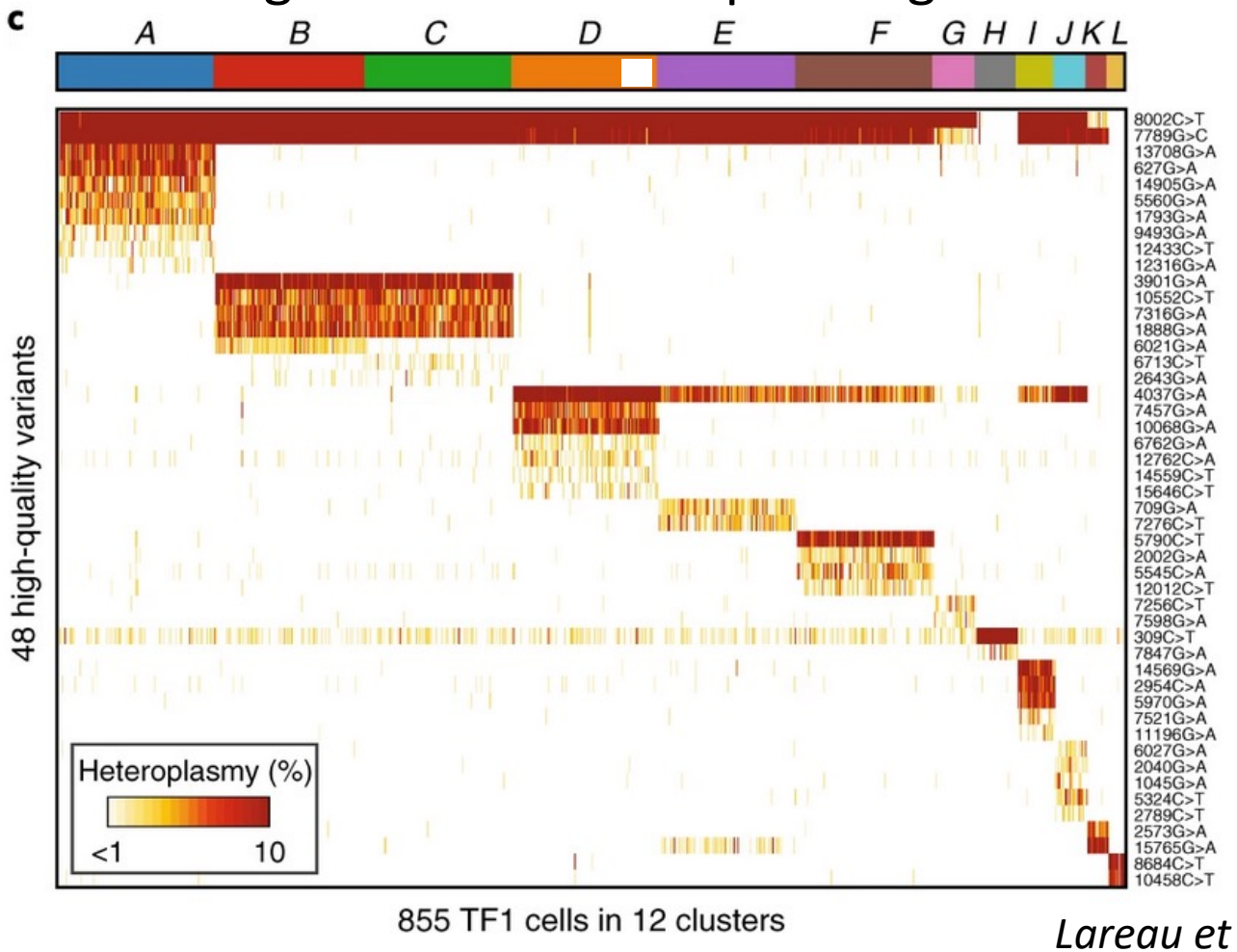


- Maternal inheritance
- mtDNA bottleneck
- Heteroplasmy shift
- Random segregation
- Purifying selection
- Threshold effect

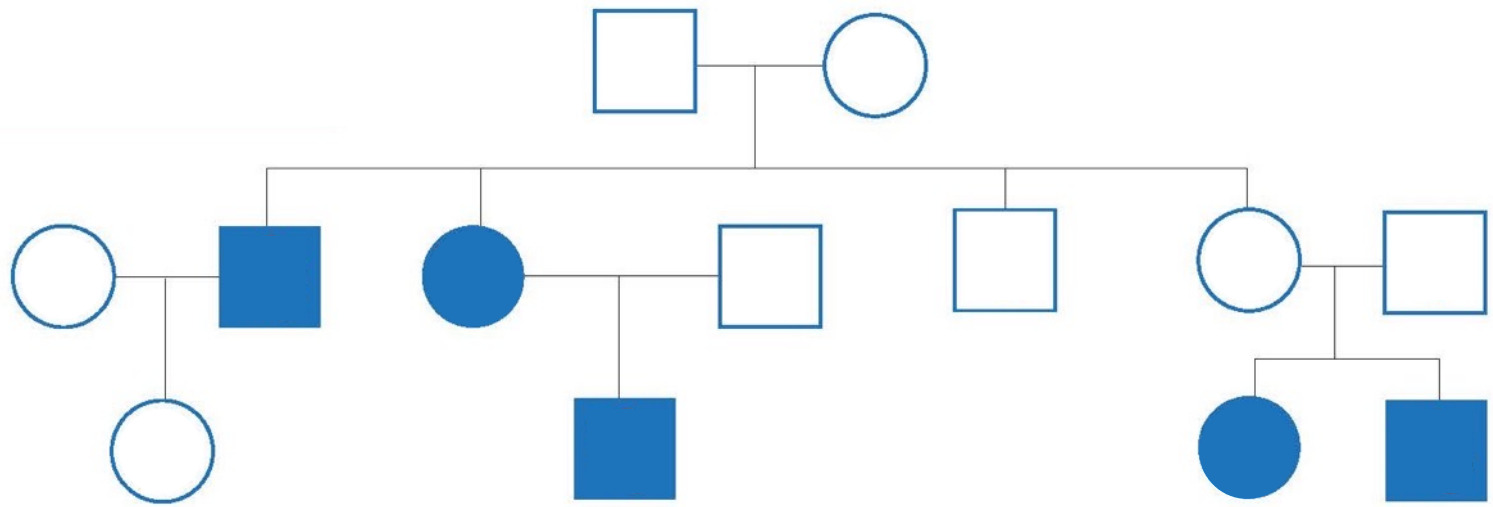
van den Ameele et al, Semin Cell Dev Biol, 2019

Novel ways to detect (universal?) heteroplasmy

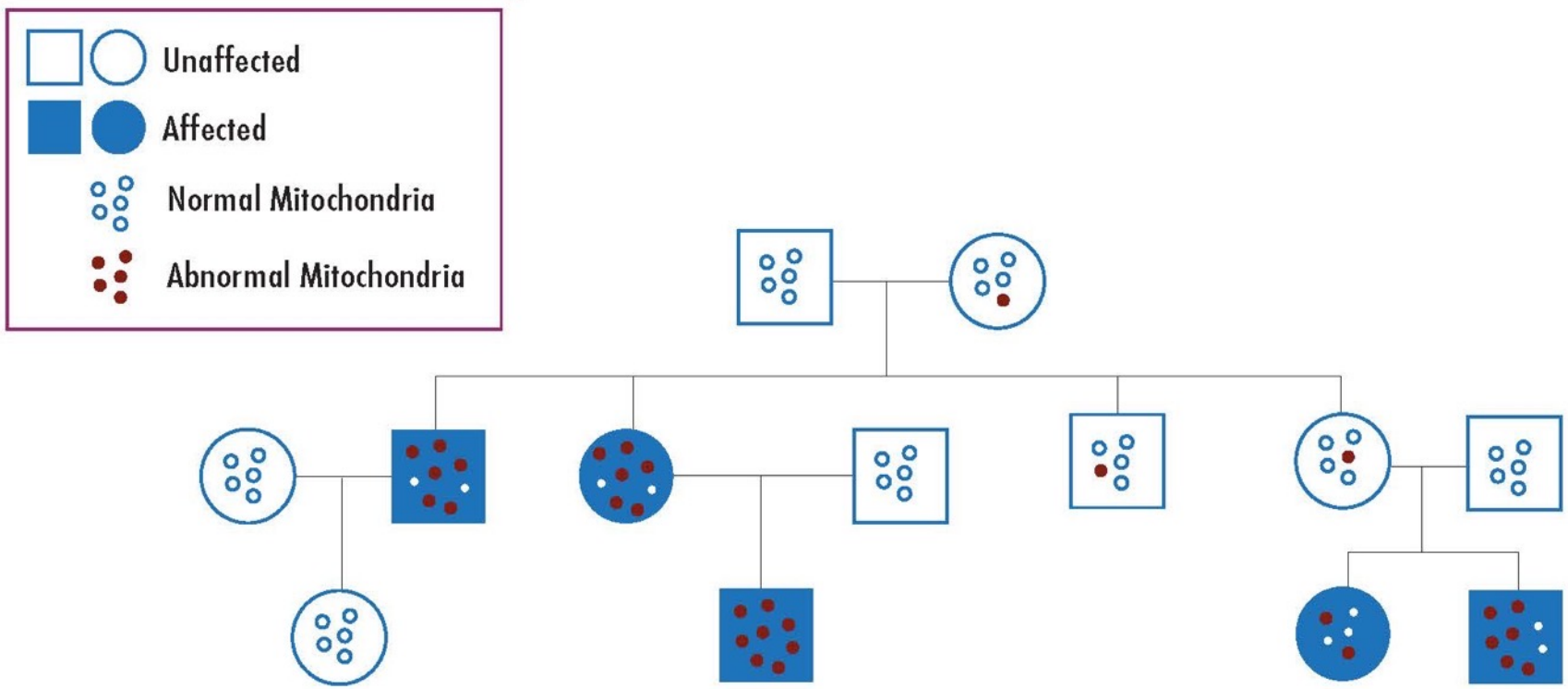
Single-cell mtDNA sequencing



Lareau et al., Nat Biotechnol, 2020.



Mitochondrial Inheritance



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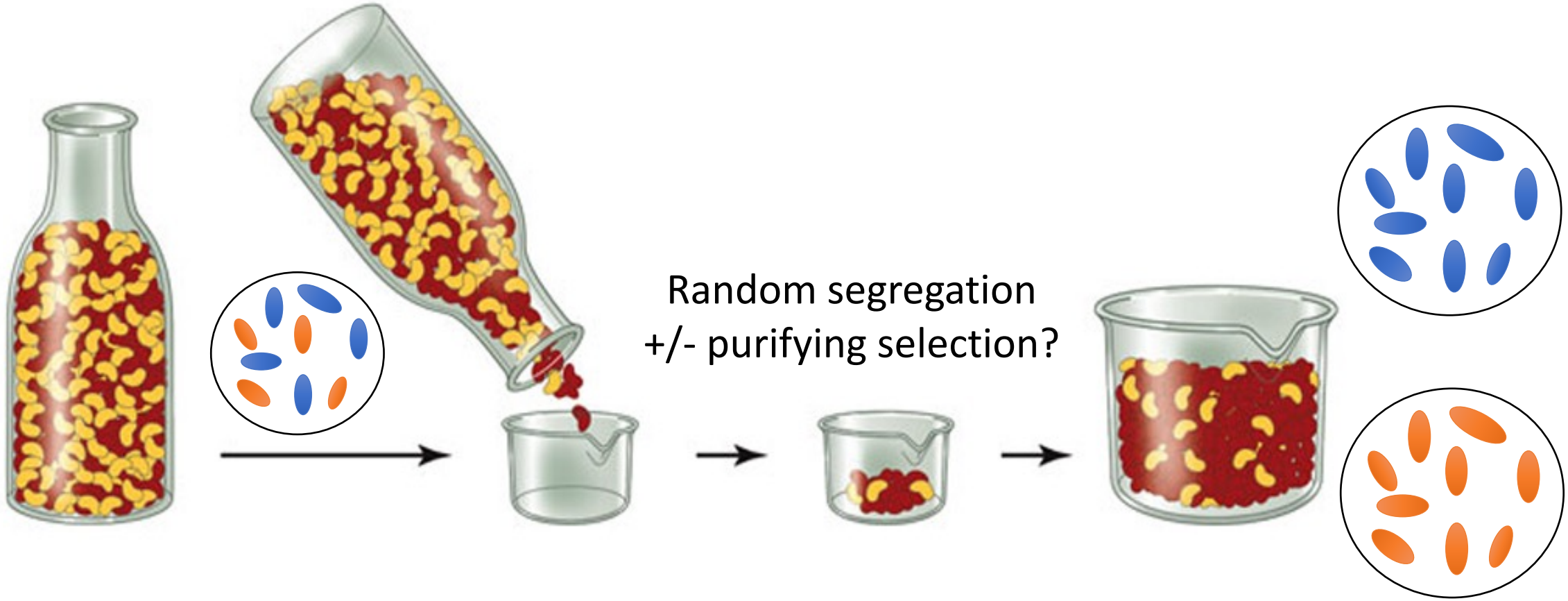
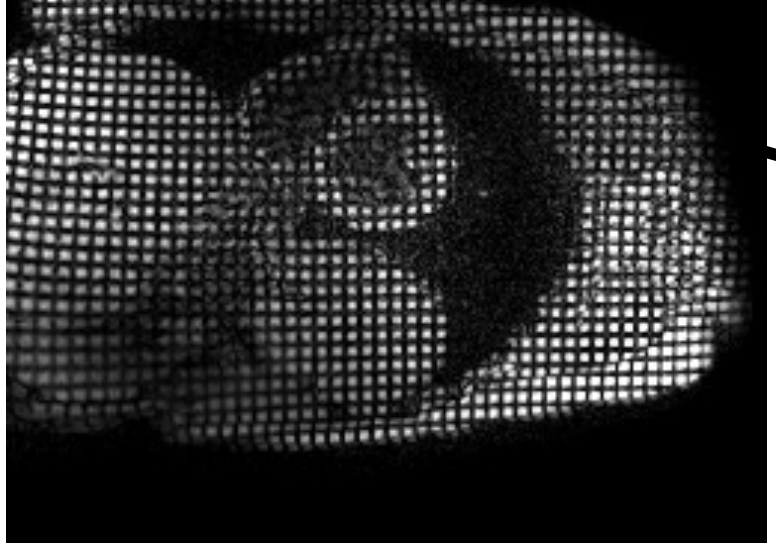
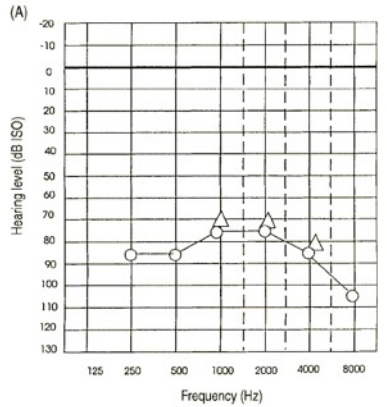
Heteroplasmy shifts over time between generations: **Mitochondrial bottleneck**



Olivo et al., *Nature* 1983





I:1 I:2

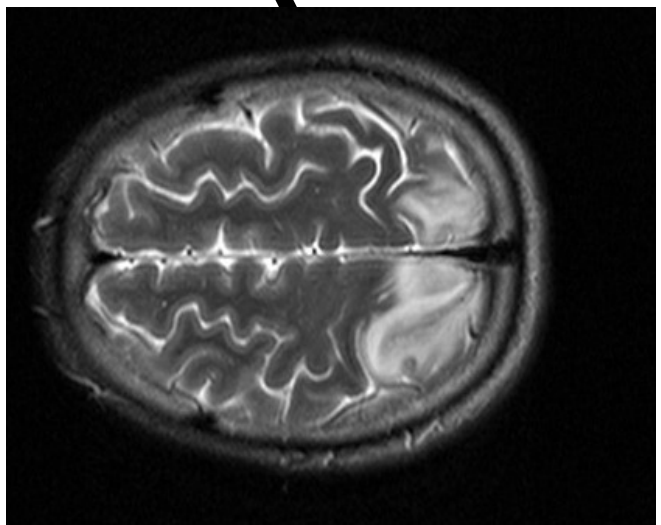
female female female

II:1 II:2 II:3 II:4 II:5 II:6 II:7

3rd TM 2nd TM < 2hrs 3rd TM 27 yrs 31 yrs 33 yrs

m.3243A>G

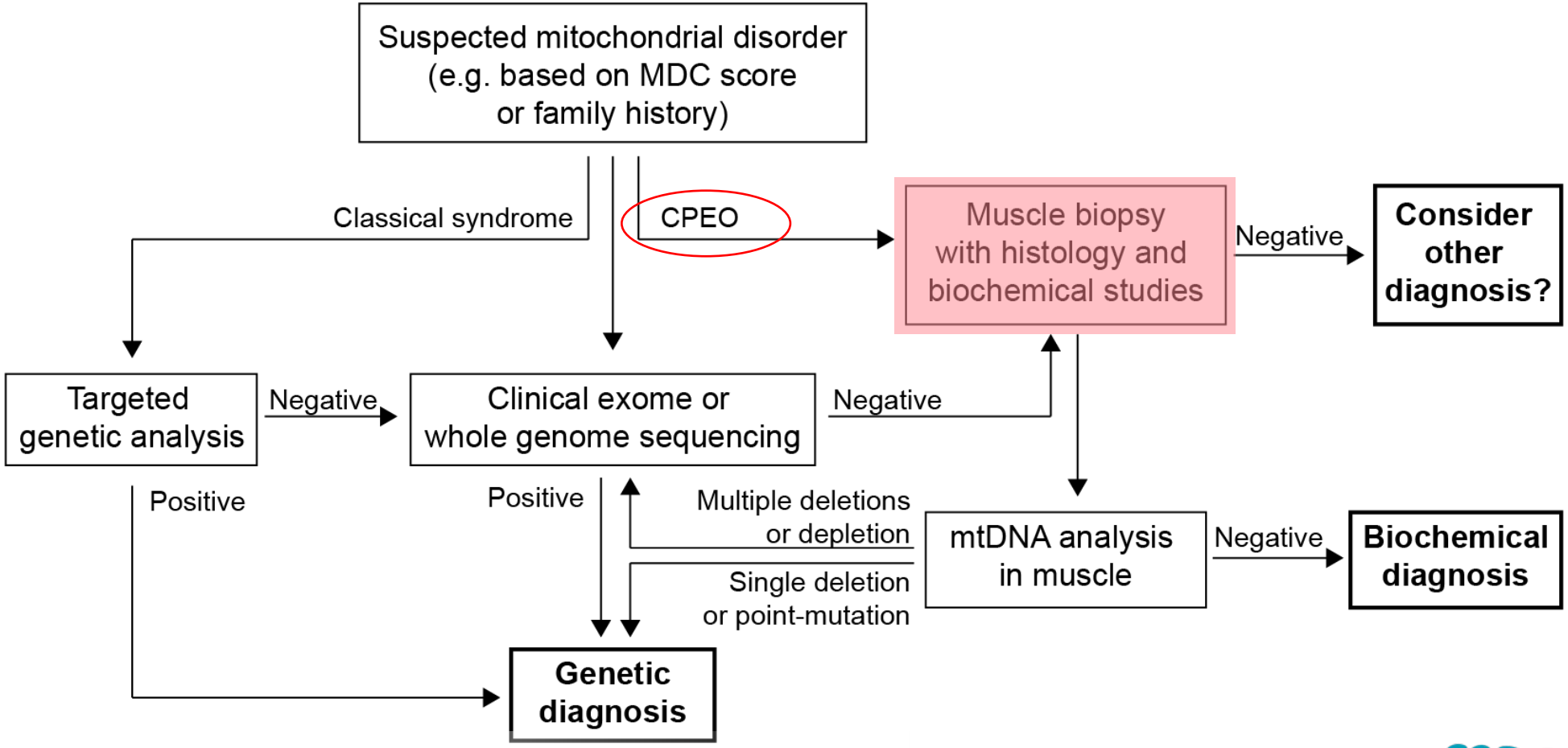
'MELAS'



(Slide from Patrick Chinnery)

Case 4: Nuclear or mitochondrial?

Approach to a patient with suspected mitochondrial disease



van den Ameele et al., in Emergencies in Neuromuscular Disorders, 2022; Schon et al., Trends in Genetics, 2021.

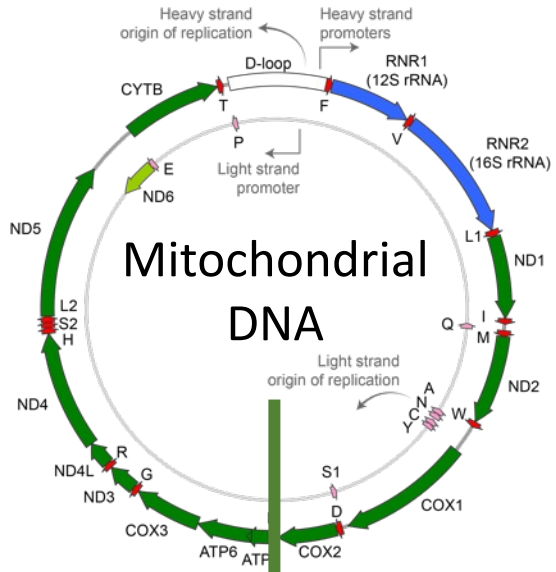
Inheritance of primary mitochondrial disease

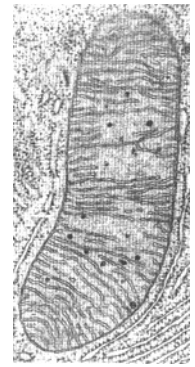
Nuclear DNA (chromosomes)

Mitochondrial DNA maintenance

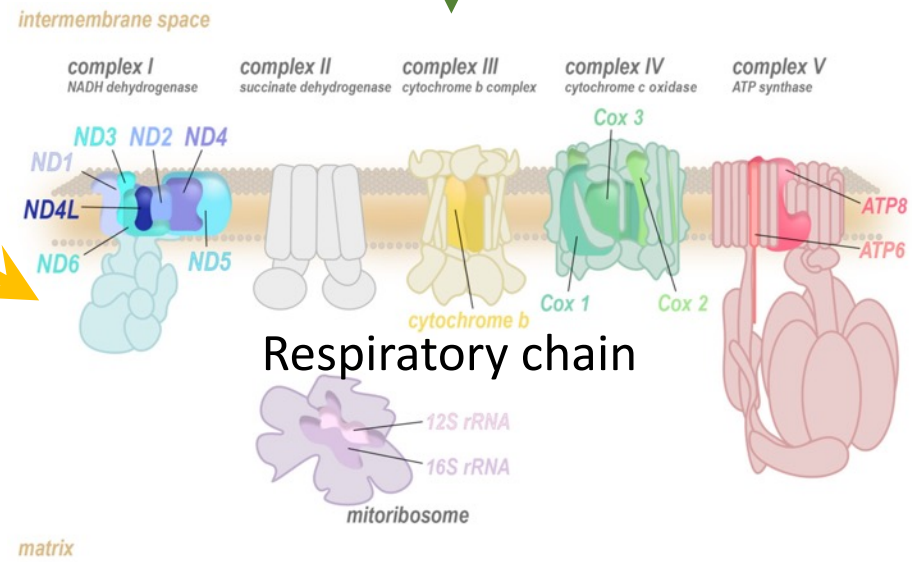
e.g. POLG, Twinkle, TYMP, **RRM2B**,…

Respiratory chain function and assembly





OxPhos Complexes I, III, IV, V (not II)



Respiratory chain

Table 2 | Defects of mtDNA maintenance

Mutated gene	mtDNA depletion	Multiple mtDNA deletions
TK2	Infantile or adult myopathy SMA phenocopy	Adult autosomal recessive PEO
DGUOK	Infantile hepato-cerebral syndrome	Adult myopathy ± PEO
PEO1	Hepato-cerebral syndrome Infantile-onset spinocerebellar ataxia	Adult autosomal dominant PEO-plus
SUCLA2	Infantile encephalomyopathy	—
SUCLG1	Infantile encephalomyopathy Methylmalonic aciduria	—
RRM2B	Infantile encephalomyopathy	Adult autosomal dominant or autosomal recessive PEO-plus
MPV17	Infantile hepatocerebral syndrome Navajo neurohepatopathy	Adult autosomal recessive PEO-plus
TYMP	Mitochondrial neurogastrointestinal encephalomyopathy	Mitochondrial neurogastrointestinal encephalomyopathy
POLG	Hepato-cerebral syndrome (Alpers syndrome)	Adult autosomal dominant or autosomal recessive PEO-plus; SANDO; MIRAS
POLG2	—	Adult autosomal dominant PEO
ANT1	—	Adult autosomal dominant PEO-plus
OPA1	—	DOA; PEO-plus
MFN2	—	DOA-plus
GFER	—	Congenital cataract, encephalomyopathy

Abbreviations: DOA, dominant optic atrophy; MIRAS, mitochondrial recessive ataxia syndrome; mtDNA, mitochondrial DNA; PEO, progressive external ophthalmoplegia; SANDO, sensory ataxic neuropathy, dysarthria and ophthalmoparesis; SMA, spinal muscular atrophy.

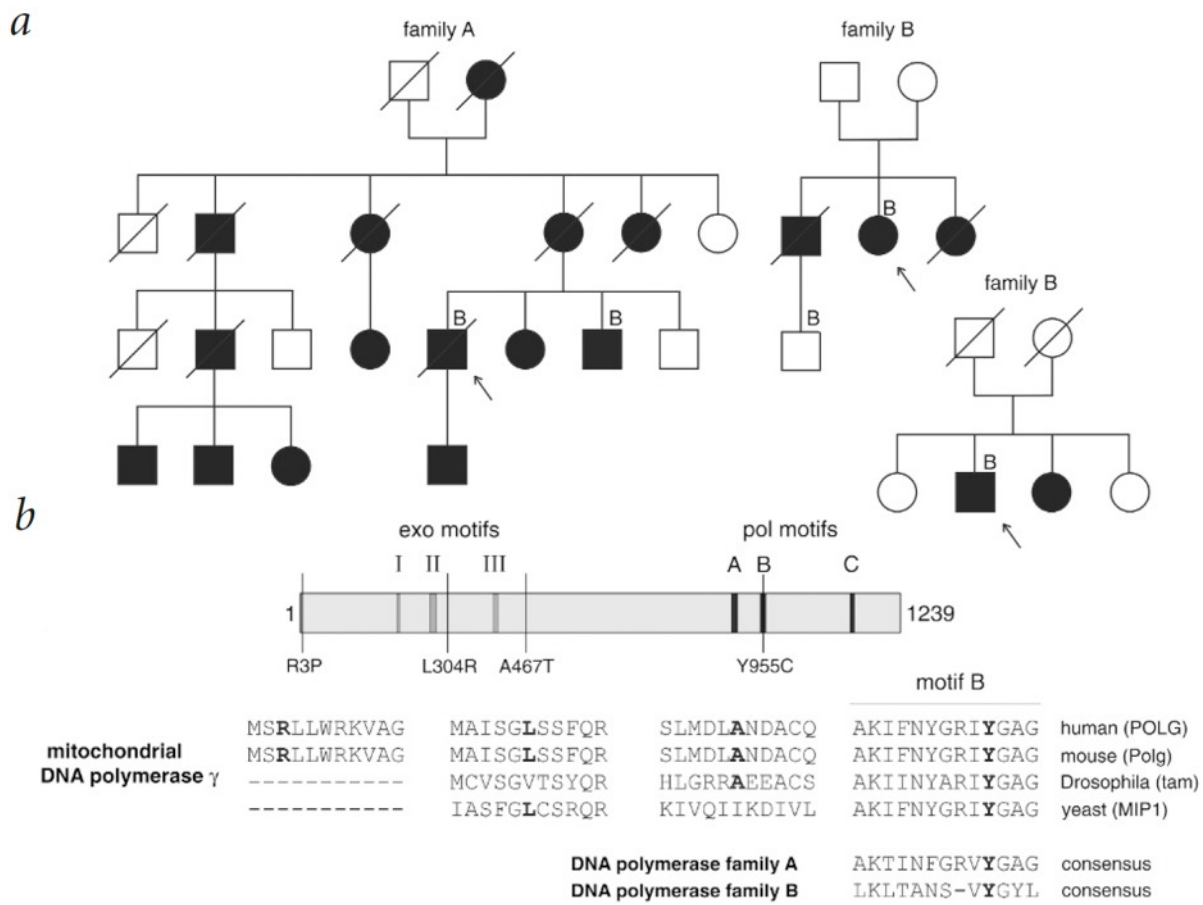
DiMauro et al, Nat Rev Neurol, 2013

Brief Communication | Published: July 2001

Mutation of *POLG* is associated with progressive external ophthalmoplegia characterized by mtDNA deletions

Gert Van Goethem, Bart Dermaut, Ann Löfgren, Jean-Jacques Martin & Christine Van Broeckhoven

Nature Genetics **28**, 211–212 (2001) | Cite this article

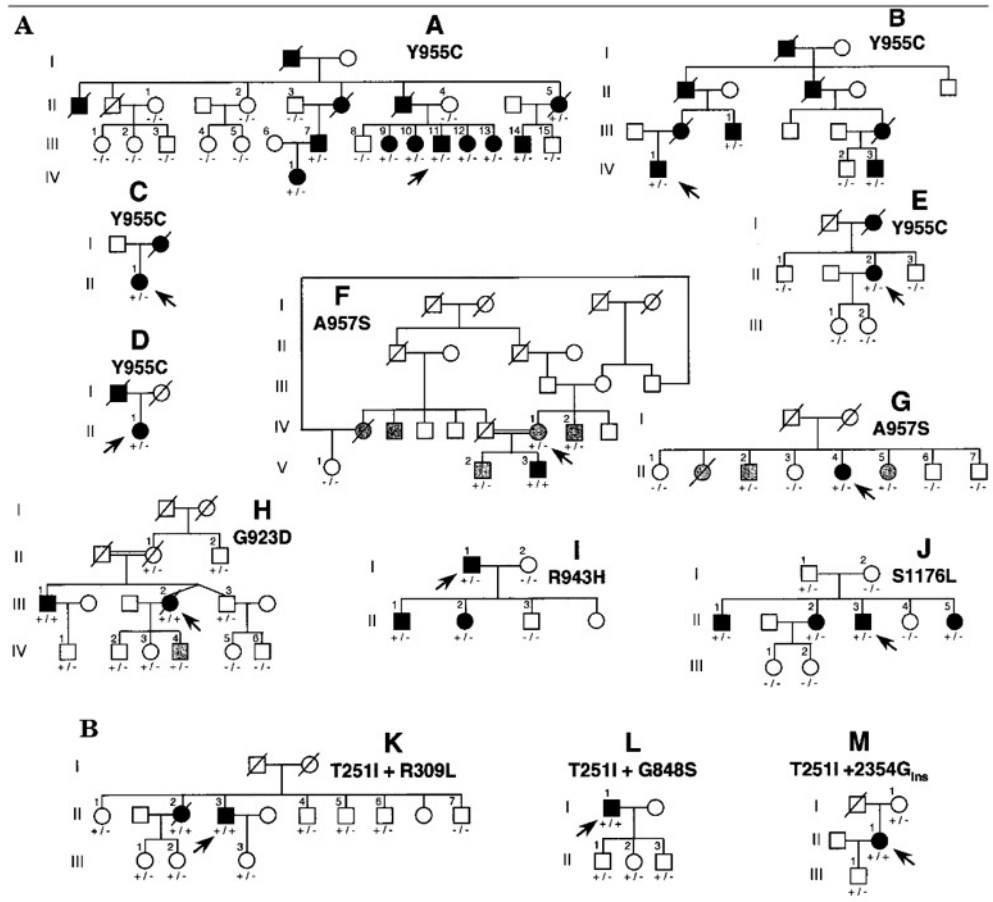


Mutations of Mitochondrial DNA Polymerase γA Are a Frequent Cause of Autosomal Dominant or Recessive Progressive External Ophthalmoplegia

Eleonora Lamantea, MSc,[1] Valeria Tiranti, PhD,[1] Andreina Bordoni, BSc,[2] Antonio Toscano, MD,[3] Francesco Bono, MD,[4] Serena Servidei, MD,[5] Alex Papadimitriou, MD,[6] Hans Spelbrink, PhD,[7] Laura Silvestri, PhD, [8] Giorgio Casari, PhD,[8] Giacomo P. Comi, MD,[2] and Massimo Zeviani, MD, PhD[1]

One form of familial progressive external ophthalmoplegia with multiple mitochondrial DNA deletions recently has been associated with mutations in *POLG1*, the gene encoding pol γA, the catalytic subunit of mitochondrial DNA polymerase. We screened the *POLG1* gene in several PEO families and identified five different heterozygous missense mutations of *POLG1* in 10 autosomal dominant families. Recessive mutations were found in three families. Our data show that mutations of *POLG1* are the most frequent cause of familial progressive external ophthalmoplegia associated with accumulation of multiple mitochondrial DNA deletions, accounting for approximately 45% of our family cohort.

Ann Neurol 2002;52:211–219



An autosomal dominant disorder with multiple deletions of mitochondrial DNA starting at the D-loop region

Massimo Zeviani*, Serenella Servidei†, Cinzia Gellera*, Enrico Bertini†, Salvatore DiMauro† & Stefano DiDonato*

* Istituto Neurologico 'C. Besta', Laboratory of Biochemistry and Genetics, 11 via Celoria, 20133 Milano, Italy
† Department of Neurology, Catholic University, viale Gemelli, 00100 Roma, Italy
‡ Department of Neurology, Columbia University, 630 West 168th Street, New York, 10032, USA

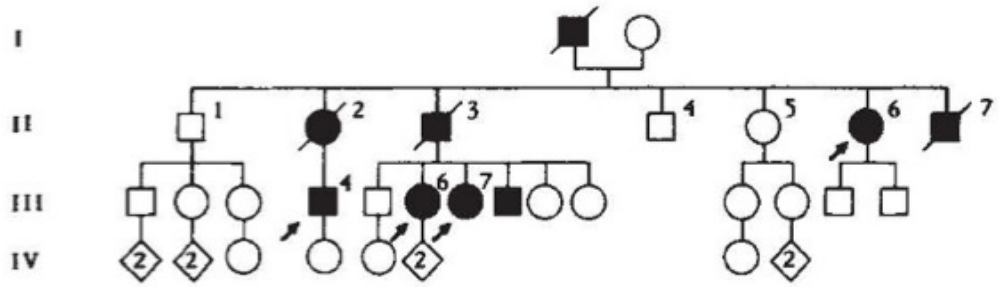
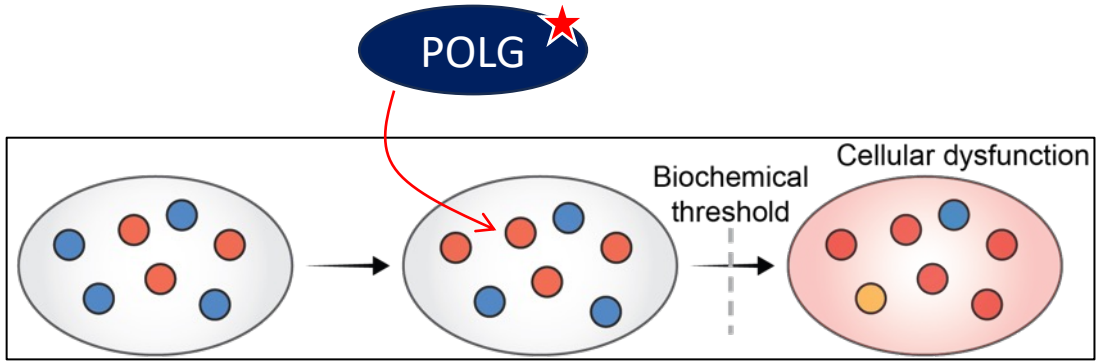


FIG. 1 Family pedigree. Solid symbols indicate clinically affected individuals. Barred symbols indicate deceased individuals. Arrows indicate the propositi. Onset of the disease is invariably in adult age. Thus, clinical attribution of the individuals in IV, who are still in infancy, is uncertain. Diamond symbols indicate siblings of unspecified sex. Number of siblings is also indicated.



van den Ameele et al., Semin Cell Dev Biol, 2019.

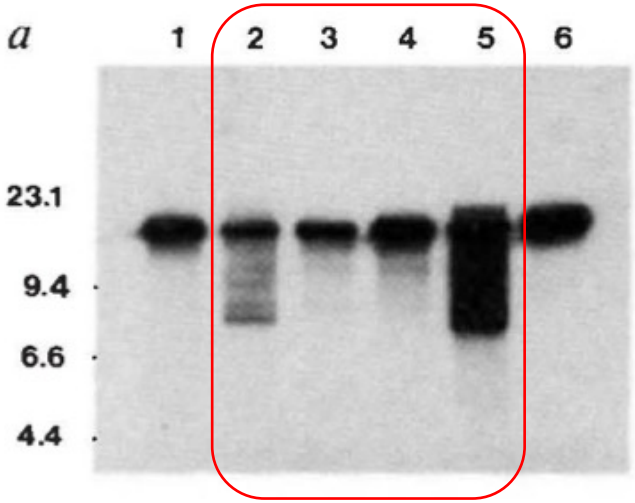


FIG. 2 *a*, Hybridization pattern of *Pvu*II-digested total human muscle DNA, probed with radiolabelled human mtDNA (for detailed description of methods see ref. 2). Lanes 1 and 6 contain samples from two unrelated control subjects, with no muscle pathology. Lanes 2–5 contain samples from the propositi: lane 2, sample from patient III-4; lane 3, sample from patient III-6; lane 4, sample from patient III-7; lane 5, sample from patient II-6 (see Fig. 1). Size is in kb. *b*, Electrophoretic pattern of mtDNA fragments amplified by PCR. DNA was separated in a 7% polyacrylamide slab gel (40:1 acrylamide: bis-acrylamide in 1 × TBE[-2]. Lane 1, patient III-4; lane 2, patient III-6; lane 3, patient III-7; lane 4, patient II-6.

METHODS. One nanogram of total cellular DNA was used in each PCR experiment. The GeneAmp kit (Perkin-Elmer) was used in all the experiments. Synthetic oligonucleotides were: 5′–TGTATTTT*AGATCT*TTTTTCC-TTCC–3′, 'forward primer' complementary to the sequence from bp 7,432 to bp 7,457 of the mtDNA L-strand[5]; 5′–TATTGTAC*GGTACC*ATAAATACTTG–3′, 'reverse primer' corresponding to the sequence from bp 16,120 to bp 16,145 of the mtDNA L-strand (restriction sites for *Xba*I in foward primer and for *Kpn*I in reverse primer are in italics). In each experiment 25 cycles were performed. Time and temperature conditions for one cycle were as follows: heat-denaturation was at 95 °C for 2 min; primer-annealing was at 52 °C for 2 min; polymerase-extension was at 72 °C for 2 min in the first 4 cycles, 3 min in the following 6 cycles, and 4 min in the final 15 cycles.

Same family as A in Lamantea et al, 2002 (AD Polg mutation) *(Serenella Servidei)*

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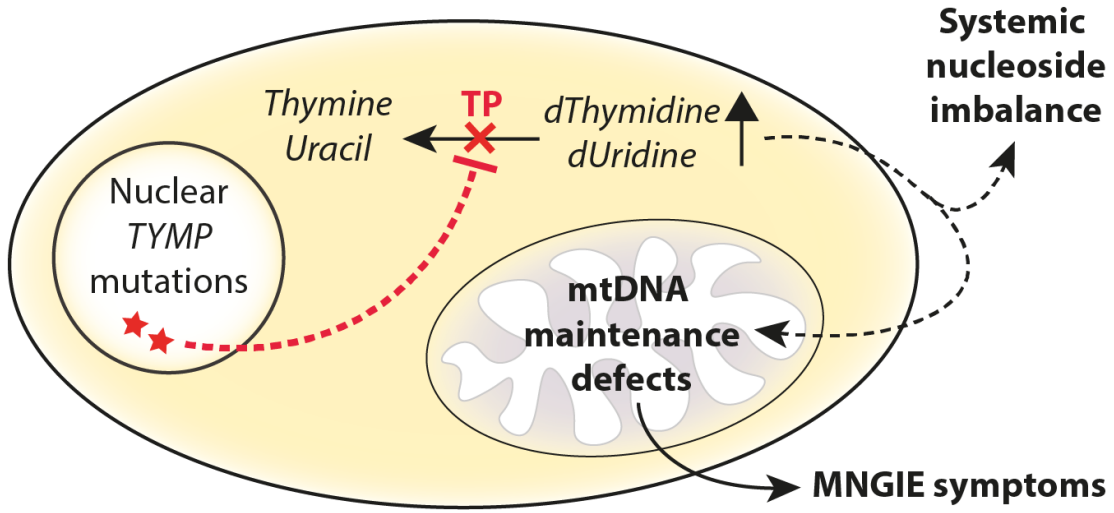
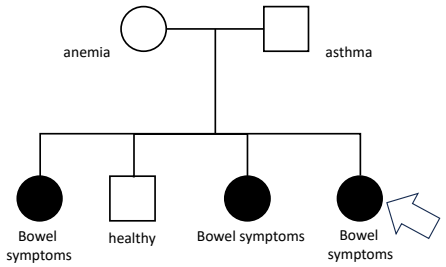
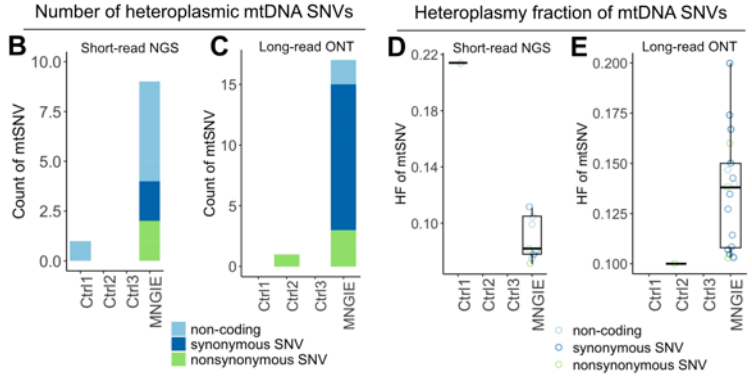
Abbreviations: DOA, dominant optic atrophy; MIRAS, mitochondrial recessive ataxia syndrome; mtDNA, mitochondrial DNA; PEO, progressive external ophthalmoplegia; SANDO, sensory ataxic neuropathy, dysarthria and ophthalmoparesis; SMA, spinal muscular atrophy.

DiMauro et al, Nat Rev Neurol, 2013

Mitochondrial Neuro-Gastro-Intestinal Encephalomyopathy (MNGIE)







MNGIE disease course

Received: 20 April 2020 | Revised: 3 August 2020 | Accepted: 5 August 2020
DOI: 10.1002/jimd.12300
REVIEW ARTICLE
JIMD SSIEM WILEY

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): Position paper on diagnosis, prognosis, and treatment by the MNGIE International Network

Gastroenterology 2019;156:1525–1527
BRIEF COMMUNICATION

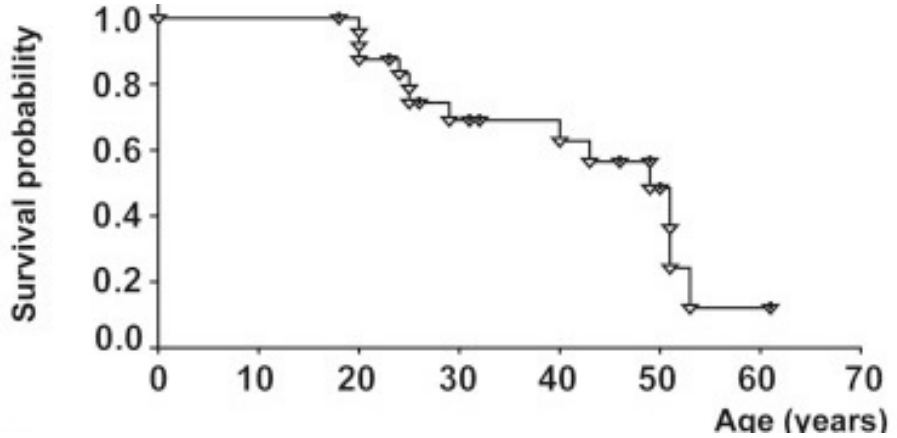
MyoNeuroGastroIntestinal Encephalopathy: Natural History and Means for Early Diagnosis

Giovanni Corazza,[1] Cécile Pagan,[2] Gaëlle Hardy,[1] Gérard Besson,[1] Anne Lombès,[3] and the investigators of the MNGIE project

[1]CHU Grenoble-Alpes, F-38000, Grenoble, France; [2]CHU Lyon, Groupement Hospitalier Est, Centre de biologie et Pathologie Est, F-69500, Bron, France; and [3]INSERM U1016, CNRS UMR 8104, Université Paris 5, F-75014, Paris, France

- Ultra-rare disease: prevalence estimated ~0.1-1/10^6
- Progressive multisystem disorder
- Mean age at onset: 17.9 years (5 months to 43 years).
- **GI symptoms** (57% at onset; 100% at diagnosis
- **Neurological symptoms** (43% at onset; 100% at diagnosis)

- **Mean age at death 35-37 years**;
  survival 100% <19 years; <5% after 50 years.
- Death is mainly due to cachexia,
  GI and liver complications



Overcoming the many hurdles between proof-of-concept and a clinical trial of a MNGIE gene therapy

Innovation Hubs for Gene Therapies

1. Funding
2. Manufacturing
3. Regulatory approvals
4. Pre-clinical toxicity and biodistribution studies
5. Natural history data
6. Phase I/II Clinical trial
7. Route to Market

MITO CAMB

Vall d'Hebron Institut de Recerca

NIHR | Cambridge Biomedical Research Centre

UKRI MRC Mitochondrial Biology Unit

CCTU Cambridge Clinical Trials Unit

UNIVERSITY OF CAMBRIDGE
Department of Clinical Neurosciences

wellcome

Cambridge Academy of Therapeutic Sciences

PIERREPONT THERAPEUTICS

LiLy

lifeArc

UNITED MITOCHONDRIAL DISEASE FOUNDATION

UK Research and Innovation

UNITED MITOCHONDRIAL DISEASE FOUNDATION®

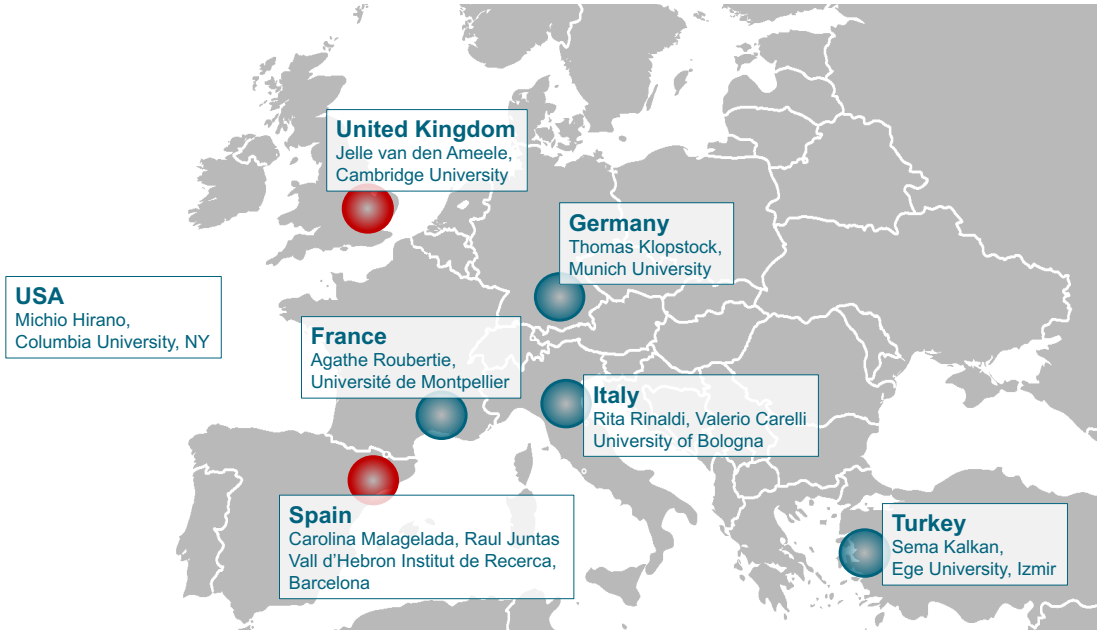
PIERREPONT THERAPEUTICS

MNGIE Natural history study

Ignazio Arena
with Caterina Garone, Bologna

Inclusion criteria

1. Have laboratory-confirmed TP deficiency:
   a) Homozygous or compound heterozygous known pathogenic mutations in the TYMP gene; and/or
   b) Decreased TP enzyme activity <20% of normal, increased plasma Thd> 2 µmol/L, or increased plasma dUrd > 5 µmol/L.
2. *Be aged 5 or over on day that study consent is obtained.*
3. *Able/willing to provide informed consent (or parent/guardian)*

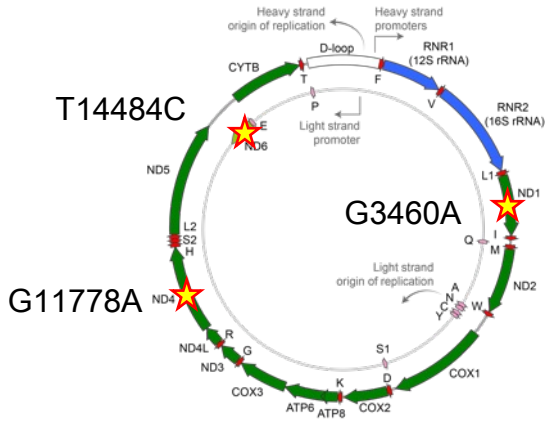


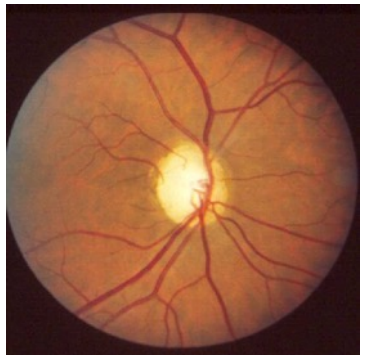
In parallel to US-based NH study led by Michio Hirano (NAMDC7402) and Genomit

Do get in touch:
jv361@cam.ac.uk
caterina.garone@unibo.it

Leber's hereditary optic neuropathy (LHON)

Credit: Lohn Eye Society Sweden

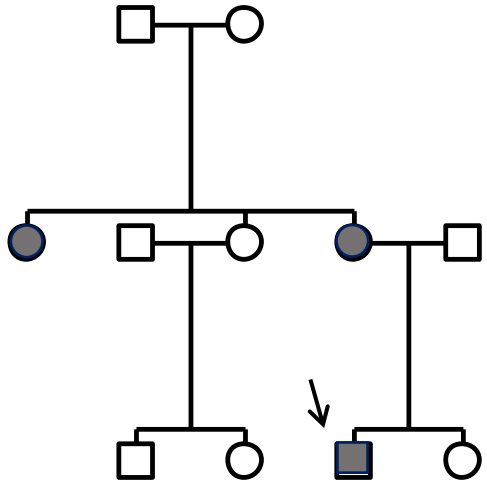


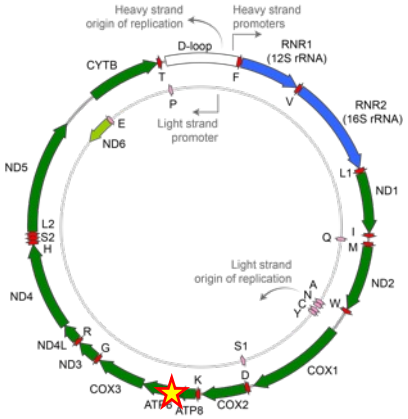


- Acute onset painless central visual loss
- One eye soon followed by the other eye
- 1/50,0000 prevalence (but 1/9,000 carriers)
- Males>Females
- Modifiers of penetrance? Smoking?
- Mostly **homoplasmic** mtDNA mutations

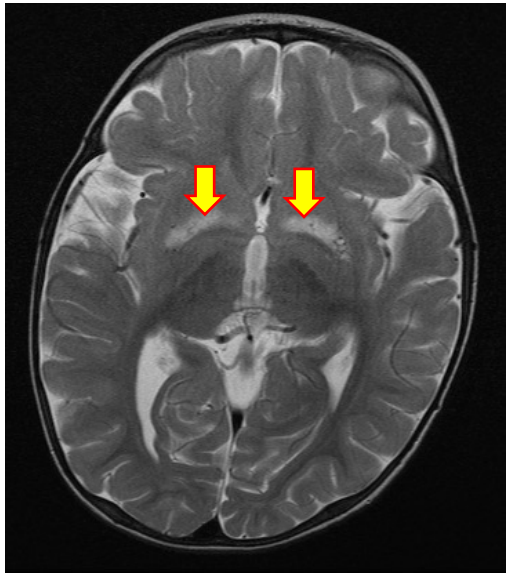
(Pictures from Patrick Chinnery)

Leigh Syndrome

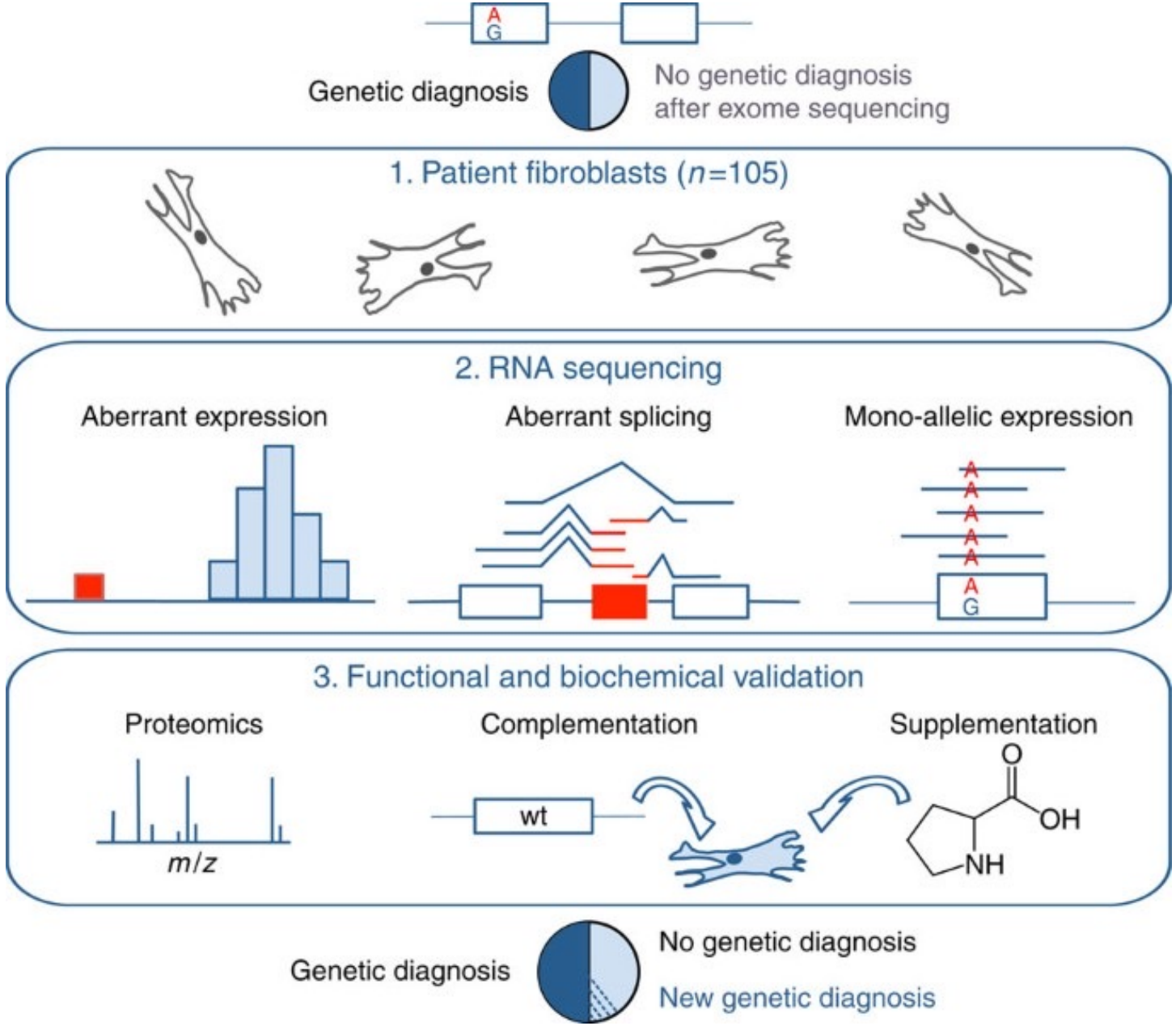




m.9176T>C (ATP6)



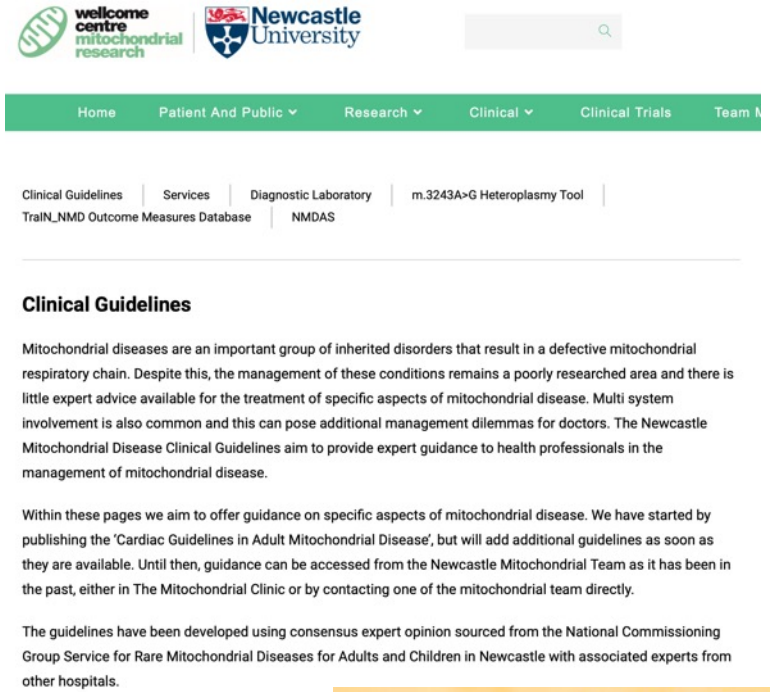
- Primarily childhood onset
- Episodic developmental regression, often triggered by metabolic stress: fever, surgery, …
- Seizures
- Movement disorder (ataxia, chorea, spasticity,…)
- Ophthalmoplegia
- Respiratory failure
- Brainstem and basal ganglia signal changes on MRI
- Broad range of genetic causes (nuclear and mtDNA)

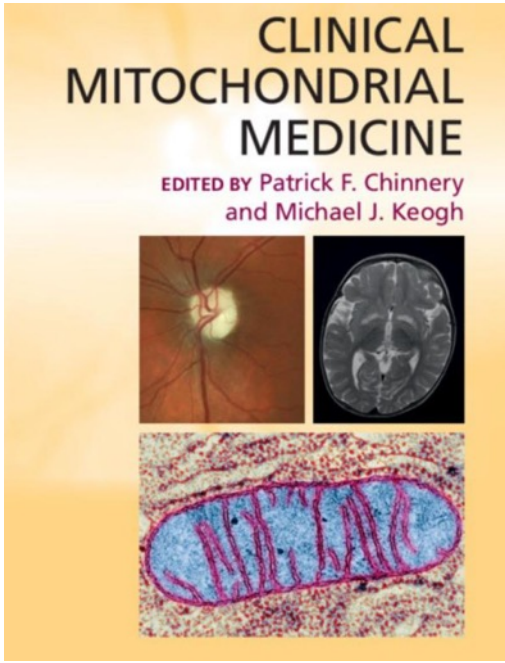


https://www.nature.com/articles/ncomms15824

Useful resources

- www-neurosciences.medschl.cam.ac.uk/mitocamb/
- www.newcastle-mitochondria.com
- Parikh et al, 2015 and 2017: Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society
- Ng et al., 2019: Consensus-based statements for the management of mitochondrial stroke-like episodes
- Chinnery and Keogh, Clinical Mitochondrial Medicine (2nd edition in preparation)





- The Lily Foundation www.thelilyfoundation.org.uk

Fighting Mitochondrial Disease.
Fighting For Hope!

Take home messages (1)

1. Mitochondria have many roles - defects in oxidative phosphorylation cause "mitochondrial disease".
2. Mitochondria contain their own circular genome that undergoes relaxed replication outside the nucleus and is maternally inherited.
3. Mitochondrial disease can be caused by mutations in the nuclear or the mitochondrial genome.
4. One cell contains many copies of mtDNA. Heteroplasmy occurs when a mutation occurs in one or more of these copies.
5. There is a threshold effect for deleterious mtDNA mutations to cause a phenotype

Take home messages (2)

6. Patterns that raise suspicion of mitochondrial disease: CPEO, diabetes and deafness, optic neuropathy, progressive multisystem conditions, maternal inheritance
7. First-line genomic testing has replaced all other diagnostic tests in most instances of suspected mitochondrial disease.
8. Sometimes, a muscle biopsy is still required, in particular in a patient with CPEO, often caused by heteroplasmic mtDNA mutations that may become undetectable in blood.
9. mtDNA maintenance disorders are nuclear inherited mitochondrial diseases due to mutations in genes required for mtDNA replication.
10. There are lots of useful resources to support diagnosis and management.

Questions?

jv361@cam.ac.uk

MRC Mitochondrial Biology Unit

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UNIVERSITY OF CAMBRIDGE
Department of Clinical Neurosciences