5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 1

Mitochondrial diseases for beginners (Level 1)

Mitochondrial diseases beyond the brain

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Mitochondrial diseases Beyond the brain

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Conflict of Interest

In relation to this presentation and manuscript:

- ❑ the Author has no conflict of interest in relation to this manuscript.
- ❑ the Author received research support from Wellcome

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Mitochondria and Mitochondrial Disease

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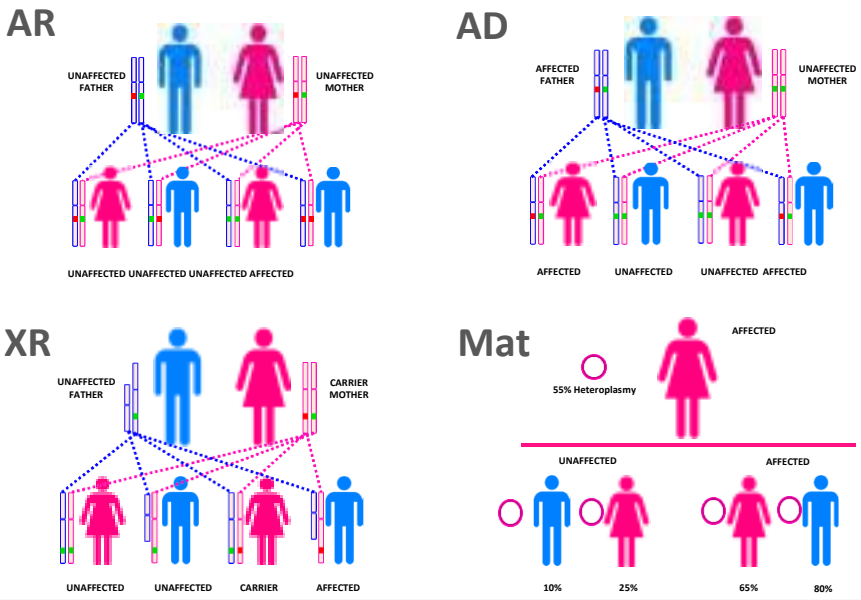
Inheritance of Mitochondrial Disease (Sporadic)



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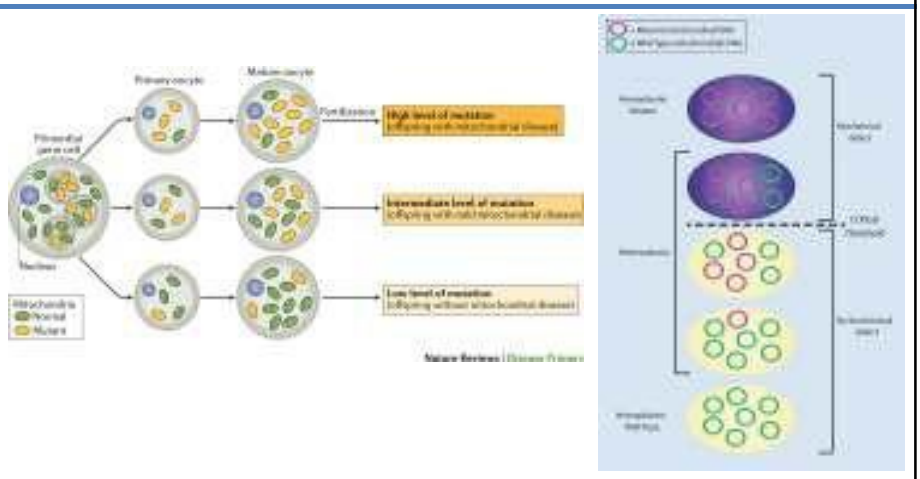
Heteroplasmy causes mitochondrial bottleneck during oogenesis



Gorman, G. S. *et al.* (2016) Mitochondrial diseases
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2016.80

Which embryo is suitable for transfer: 18% heteroplasmy, cut-off value of current PGD embryo transfer practice guidelines

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How common is Mitochondrial Disease?

Minimum point prevalence (mtDNA mutations): 1, in 5,000
Overt disease due to nDNA mutations: 2.9 per 100,000
Prevalence (total): 1 in 4,300

Mutation	Affected per 100,000 (CI)	'At Risk'
LHON	3.7 (2.9-4.6)	4.4 (3.7-5.3)
m.3243A>G	3.5 (2.7-4.4)	4.4 (3.7-5.3)
mtDNA deletion	1.5 (1.0-2.1)	0
m.8344A>G	0.2 (0.1-0.5)	0.5 (0.2-0.8)
SPG7, ar	0.8 (0.5-1.3)	1.3 (0.9-1.8)
PEO1, ad	0.7 (0.4-1.2)	2.3 (1.7-2.9)
OPA1, ad	0.4 (0.2-0.7)	0.7 (0.4-1.1)
POLG, ar	0.3 (0.1-0.6)	0.3 (0.1-0.6)
RRM2B, ad	0.2 (0.1-0.5)	0.7 (0.4-1.0)
nDNA (GD)*	0.2 (0.1-0.5)	0.3 (0.1-0.6)

*Genetically undetermined

Gorman *et al* 2015 Annals of Neurology

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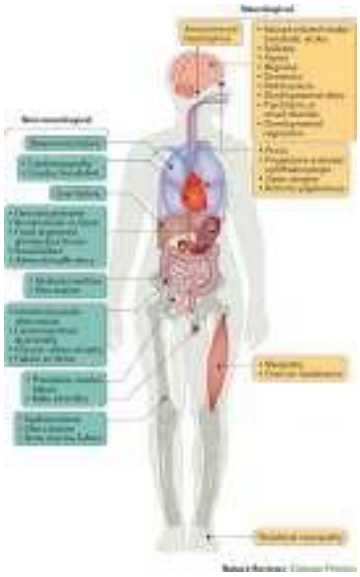
Clinical presentations of Mitochondrial Disease



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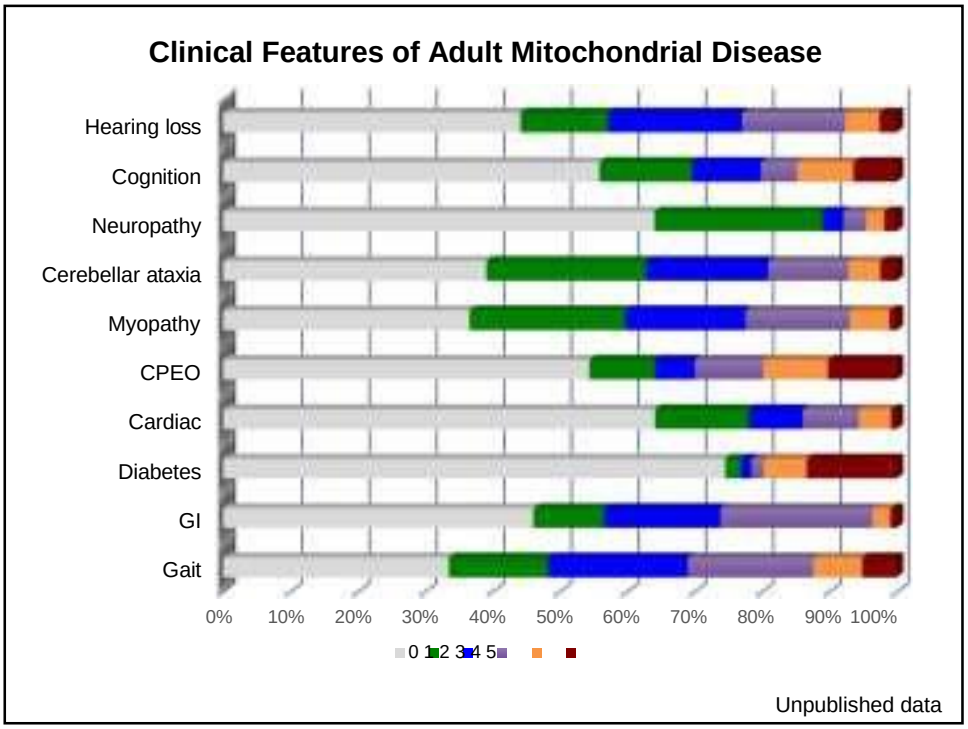
Clinical Features of Adult Mitochondrial Disease
Hearing loss
Cognition
Neuropathy
Cerebellar ataxia
Myopathy
CPEO
Cardiac
Diabetes
GI
Gait
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
0 1 2 3 4 5
Unpublished data

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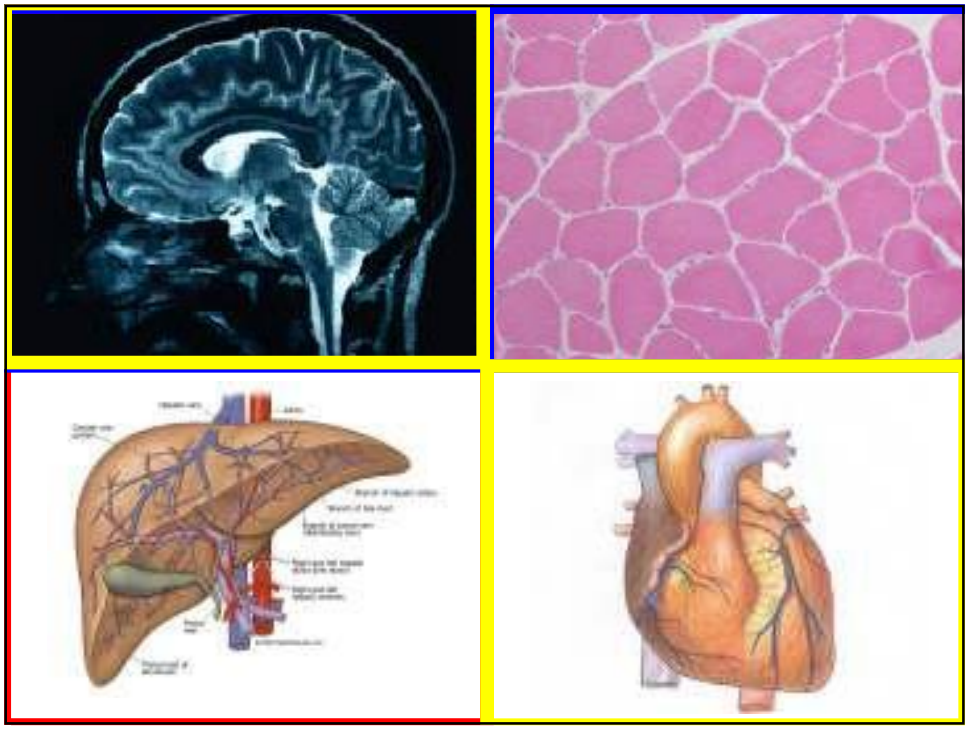

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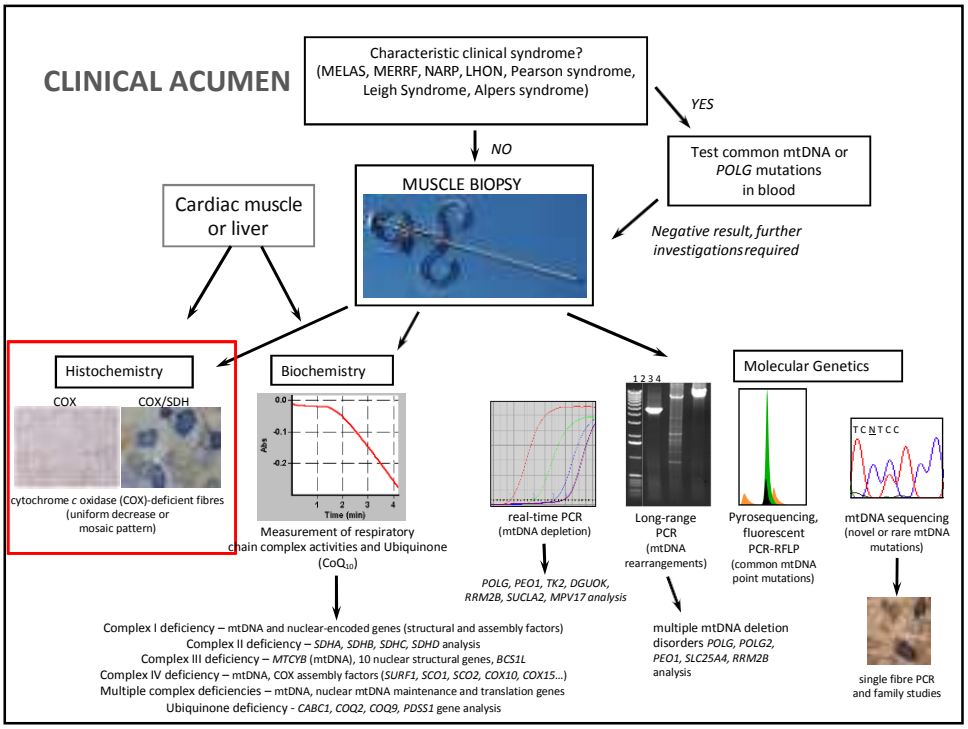

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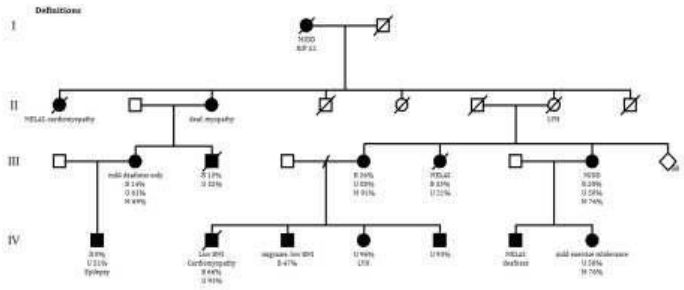
Clinical heterogeneity within families



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Same Genotype: Different Phenotype

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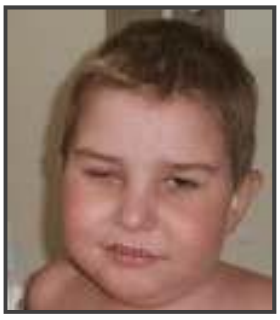

Ophthalmoplegia
Short stature
Deafness
Myopathy
Cardiac conduction defect [pacemaker]
Diabetes
Adrenal failure
Died age 7

Ophthalmoplegia
Short stature
Deafness
Myopathy
Cardiac conduction defect
Aged 44

Ophthalmoplegia
Aged 68

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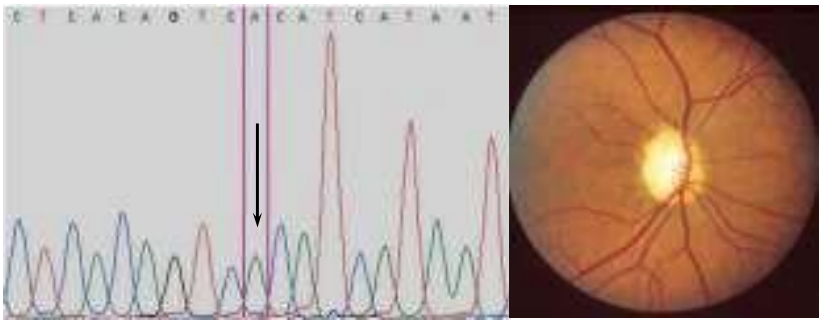
Leber's Hereditary Optic Neuropathy (LHON)



11778G>A, *MTND4*

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Dystonia Phenotype

Dystonia and Complex I Deficiency: m.11778G>A

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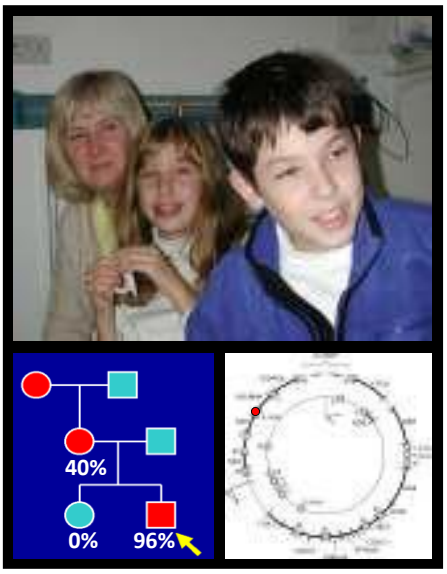
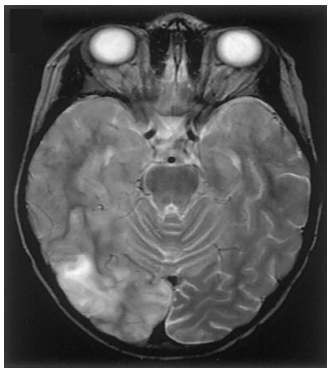
m.3243A>G *MTTL1*





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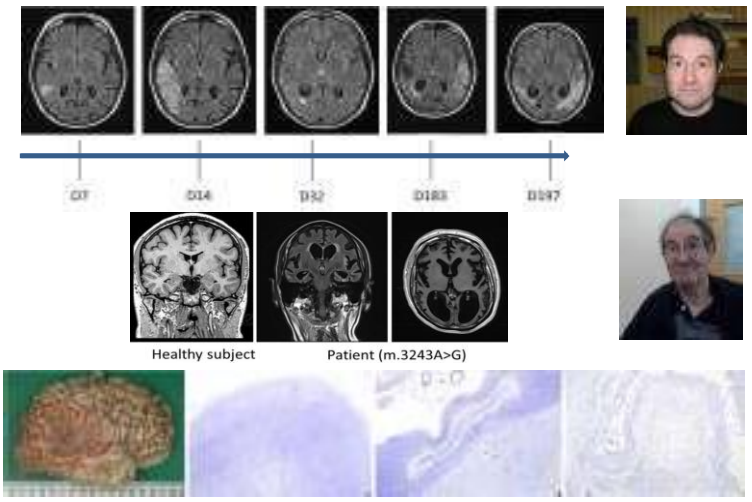
Seizures and Stroke-like episodes



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m.3243A>G *MTTL1*

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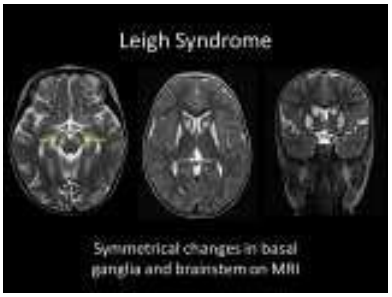
Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society
AMERICAN NEUROLOGICAL ASSOCIATION

Review

Leigh syndrome: One disorder, more than 75 monogenic causes

Nicole J. Lake MSc, Alison G. Compton PhD, Shamima Rahman MD, PhD, David R. Thorburn PhD

First published: 27 October 2015 | https://doi.org/10.1002/ana.24551 | Cited by: 96



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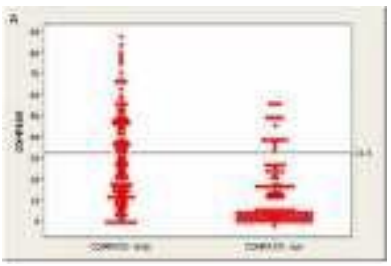
Original Paper

Novel *MTND1* mutations cause isolated exercise intolerance, complex I deficiency and increased assembly factor expression

Grainne S. Gorman*†‡, Emma L. Blakely*‡, Hue-Tran Hornig-Do*‡,², Helen A.L. Tuppen*, Laura D. Greaves*, Langping He*, Angela Baker*, Gavin Falkous*, Jane Newman*†, Michael I. Trenell*†, Bryan Lecky§, Richard K. Pettyl, Doug M. Turnbull*, Robert McFarland* and Robert W. Taylor*



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Ptosis and CPEO

m.3243A>G

m.8344A>G

SLSD of mtDNA (KSS)

SLSD of mtDNA

POLG (AR)

PEO1 (AD)

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CPEO Chronic Progressive Ophthalmoplegia

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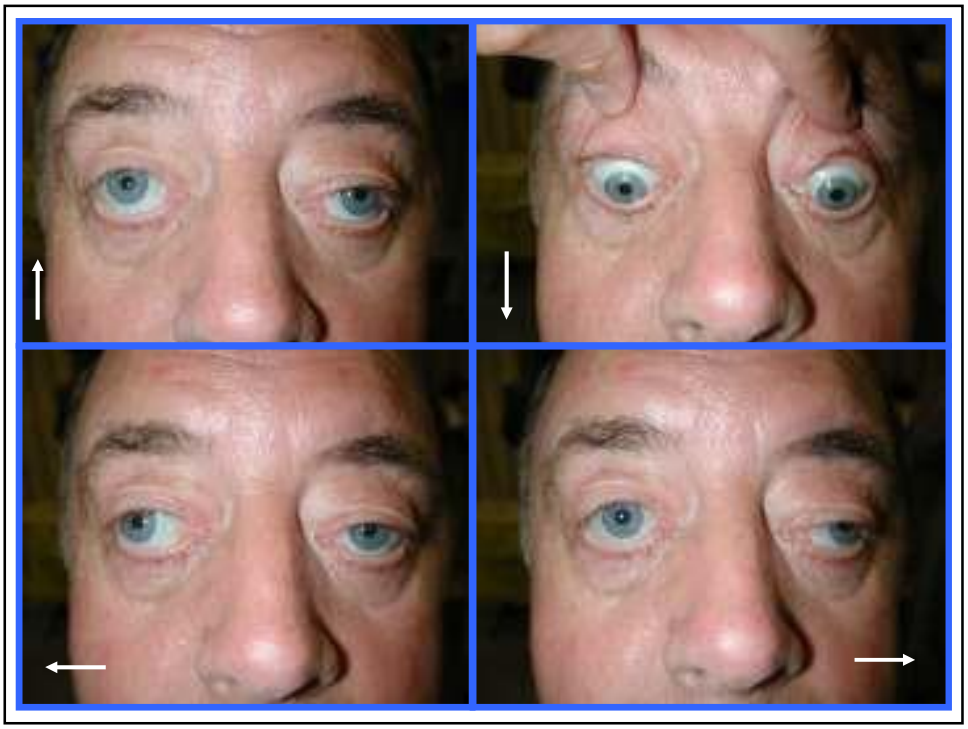

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CPEO

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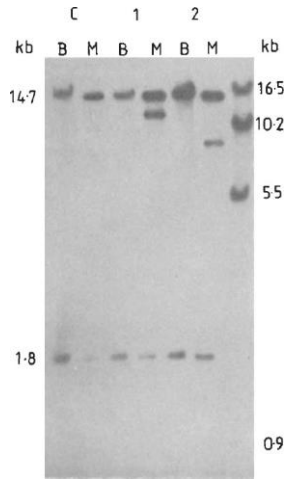
Deletions of muscle mitochondrial DNA in patients with mitochondrial myopathies

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

Department of Clinical Neurology, Institute of Neurology, Queen Square, London WC1N 3BG, UK



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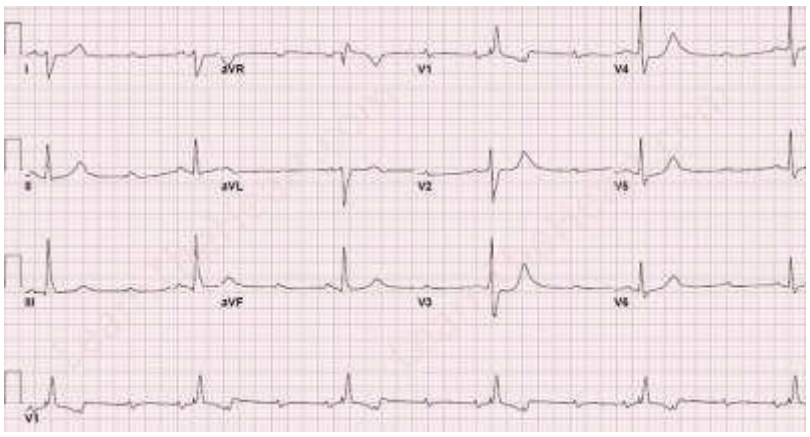

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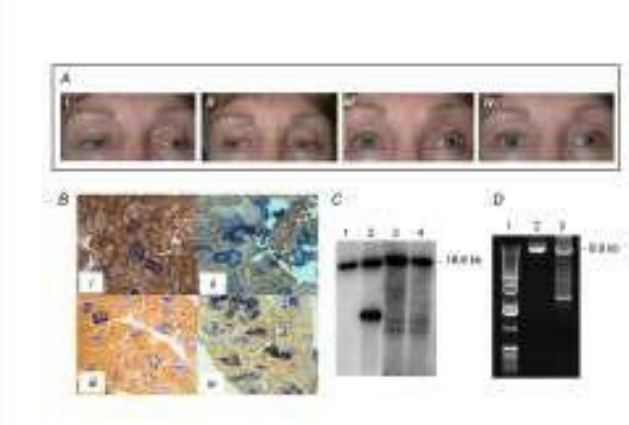
Clinical, histochemical and mtDNA abnormalities



A, Typical clinical features of a patient with mitochondrial PEO; the patient is asked to look left (i), right (ii), up, (iii) and down (iv). B, Sequential COX-SDH histochemisty of representative diagnostic muscle biopsies showing the presence of scattered COX-deficient fibres in patients with various disorders of adult-onset mtDNA maintenance abnormalities including (i) recessive (homozygous p.(Ala467Thr)) POLG mutations; (ii) a dominant, heterozygous p.(Gln458His) *C10ORF2* mutation; (iii) recessive (p.(Arg186Gly) and p.(Thr218Ile)) RRM2B mutations; (iv) recessive (p.(Asn288*) and p.(Lys558*)) SPG7 mutations; (C) Southern blotting of muscle DNA showing a control (lane 1), a single, large-scale mtDNA deletion (lane 2) and the typical banding pattern observed with multiple mtDNA deletions (lanes 3 and 4); (D) Long-range PCR also indicating the presence of multiple mtDNA deletions (lane 3) alongside a control (lane 2) and size markers (lane 1).

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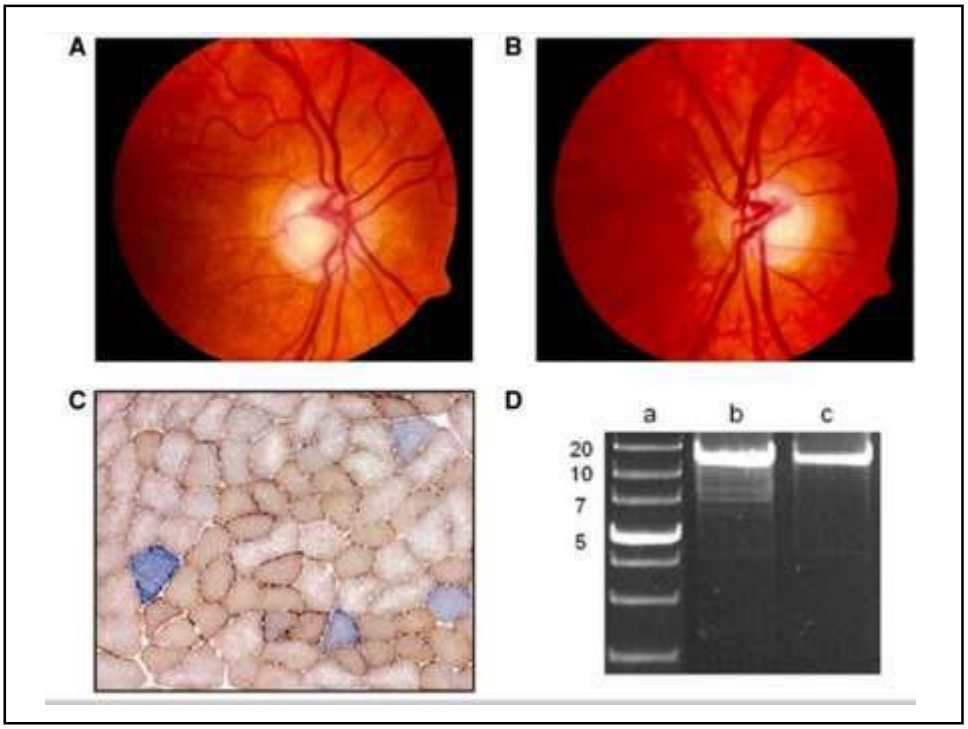

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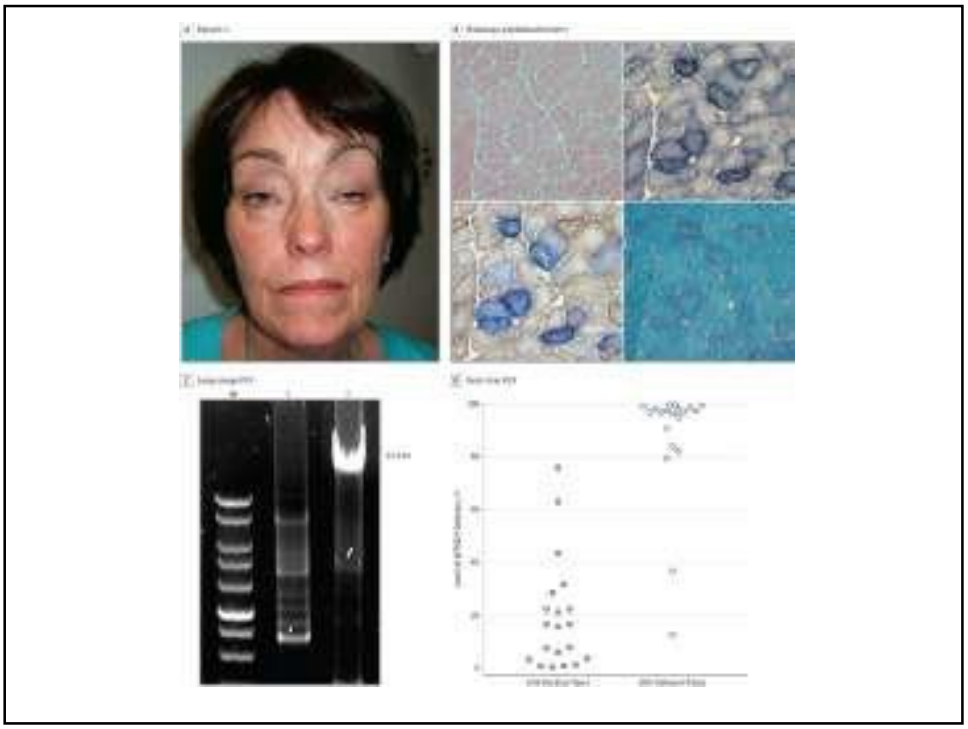

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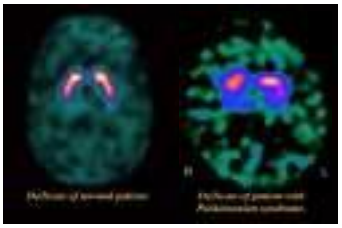

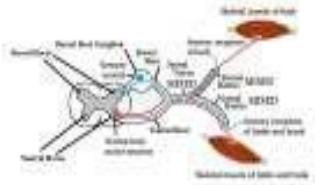

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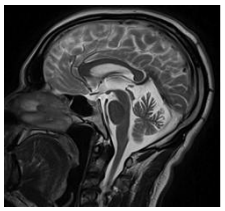

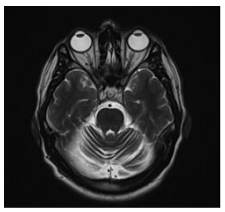

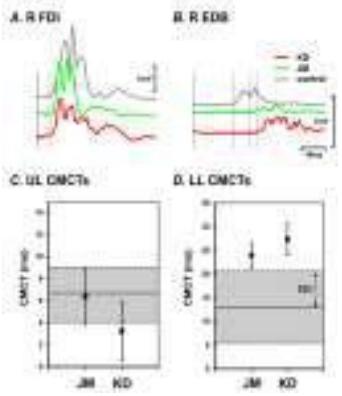

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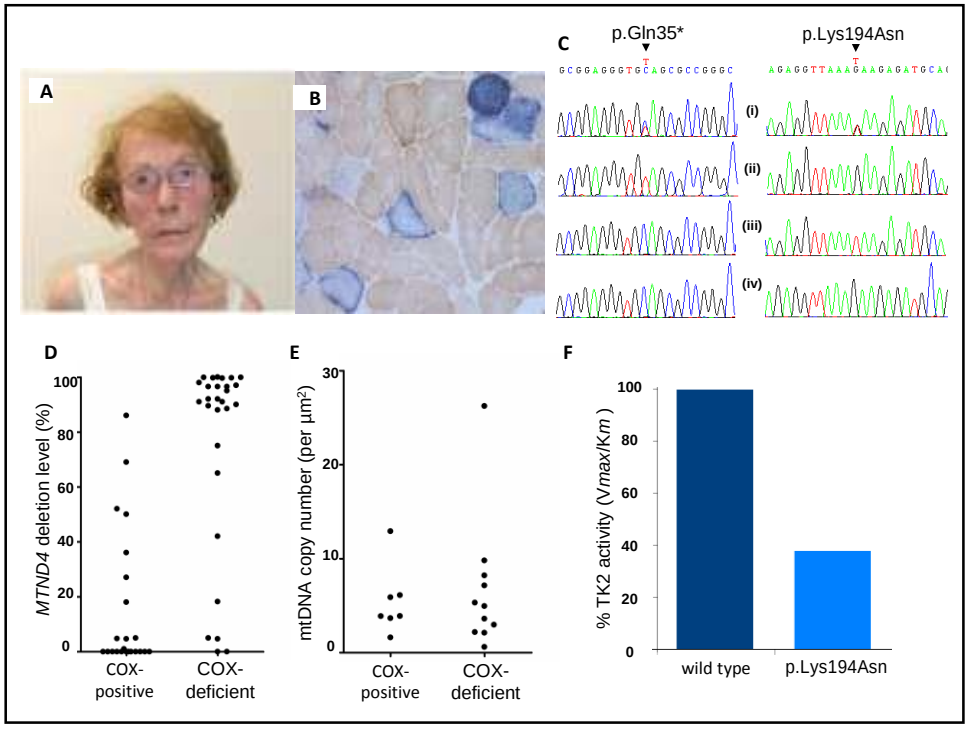

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Acute setting 74 yo

- Ptosis (marked)
- CPEO (mild)
- Bilateral facial weakness
- Dysarthria; bulbar weakness (mild)
- Proximal muscle weakness
- Diaphragmatic weakness
- Areflexia

- Arterial blood gas: Type II resp failure
  - CO2:
  - pO2:9.97
  - Nocturnal hypoventilation

- EMG/NCS:
  - SMAN
  - Mild myotonic features

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Optic atrophy
Parkinsonism
Swallowing difficulties
Pure CPEO
Respiratory failure
Spasticity

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OPA1


POLG


RRM2B


PEO1


TK2


SPG7

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Systems based approach: **case reports**

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Endocrine and Diabetes

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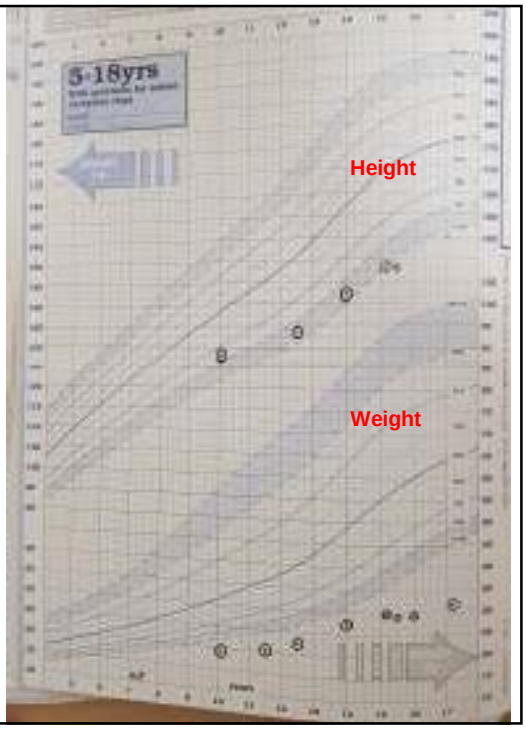
Short stature and low BMI



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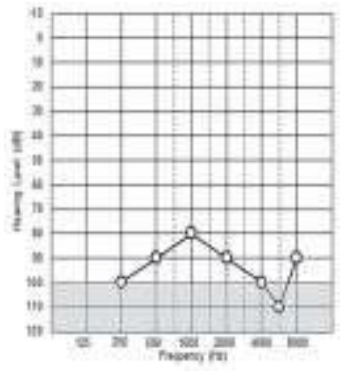
Tinnitus and Deafness



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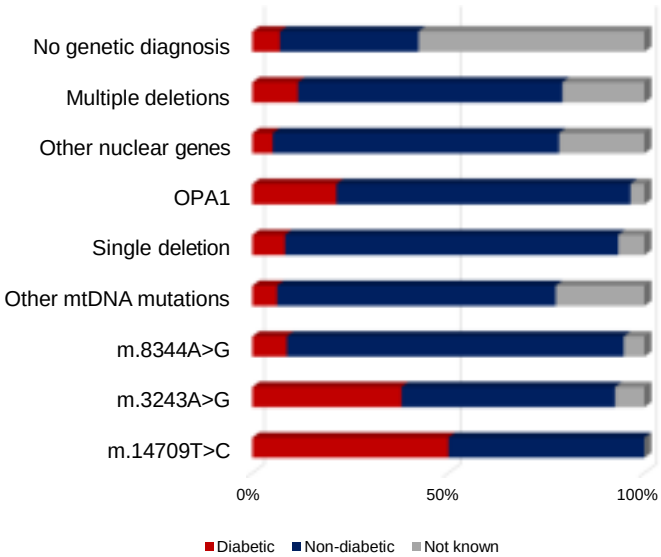
Genotype and Diabetes



Unpublished data

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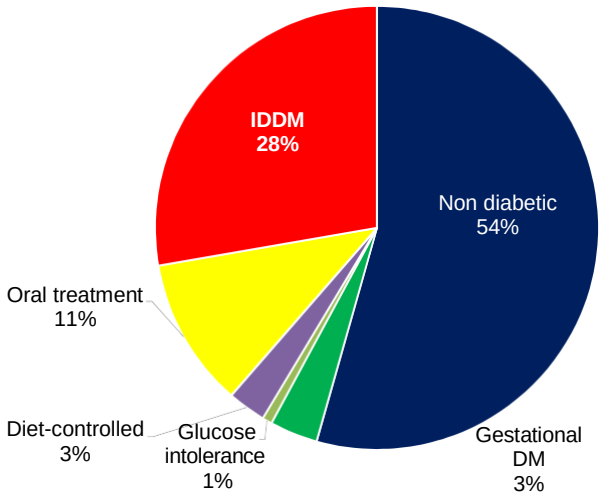
m.3243A>G and Diabetes



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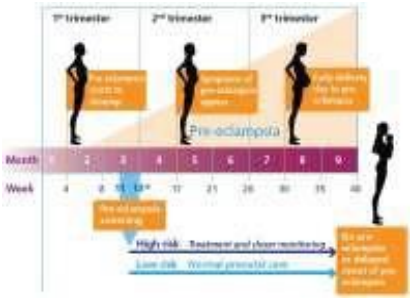
Mitochondrial disease and pregnancy



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Monitoring and Diabetes

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Cardiac and phenotypes

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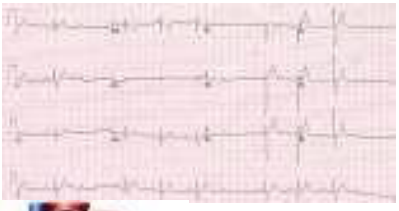
Cardiac Phenotype

mtDNA

- m.1624C>T *MTTV*
- m.3243A>G *MTTL1*
- m.3260A>G *MTTL1*
- m.3303C>T *MTTL1*
- m.4269A>G *MTTI*
- m.4295A>G *MTTI*
- m.4300A>G *MTTI*
- m.4317A>G *MTTI*
- m.4320C>T *MTTI*
- m.8296A>G *MTTK*
- m.8344A>G *MTTK*
- m.8348A>G *MTTK*
- m.8529G>A *MTATP8*
- m.9997T>C *MTTG*
- m.12192G>A *MTTH* (Dilated)
- m.12297T>C *MTTL2* (Dilated)
- m.13513G>A *MTND5*
- m.15243G>A *MTCYB*
- m.15498G>A *MTCYB*

Large single deletion (KSS)



nDNA

- *SCO2*
- *COX15*
- *NDUFA2*
- *NDUFS2*
- *NDUFV2*
- *SLC25A3*
- *SLC25A4*
- *ATPAF2*

TAZ1 (*G4.5*)

FRDA (Frataxin)

TK2

AGK

AARS2

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Cardiac Involvement in the Mito Cohort (Newcastle)

- 18% (n=78)
- It is more prevalent in mtDNA mutations than common nuclear genes.

Genotype	Prevalence
m.3243A>G	25%
m.8344A>G	26%
Single deletion	15%
POLG	1/21
PEO1	0
RRM2B	1/15

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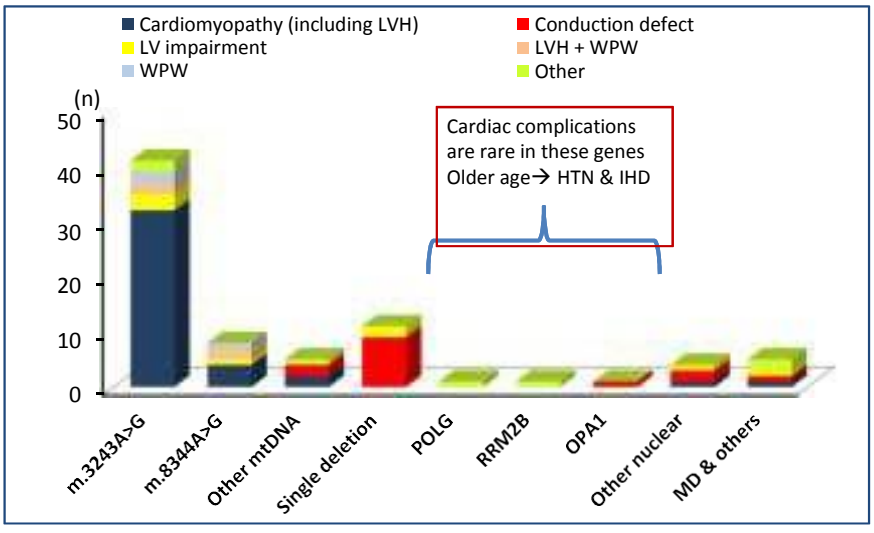
Genotype-specific Cardiac Involvement



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Cardiac and Cases 1

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Sudden Adult Death Syndrome (SADS) in Asymptomatic m.3243A>G Carriers

30 year old male
- m.3243A>G mutation carrier (family screening)
- Fit & well, went to gym regularly
- Night out with friends and consumed some alcohol
- Found dead at home on the following day

33 year old female
- m.3243 mutation carrier (family screening)
- Full time teacher, referred for discussion of PGD. Mild LVH on cardiac screening
- Went out with friends, found dead at home next day

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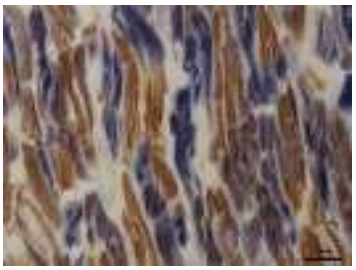
	Case 1	Case 2
Histochemistry		
Cardiac muscle	40-60% COX deficiency	15-20% COX deficiency
Skeletal muscle	20-30% COX deficiency	25%
Heteroplasmy level		
Cardiac muscle	91-95%	76-78%
Skeletal muscle	83-85%	90%
Brain tissue	90%	79-85%



Acknowledgement: Gavin Falkous & Nichola Lax

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How common is SADS in m.3243A>G?

Review of historical cases and family pedigree = 6 possible cases; most recent suspected SADS case occurred in Dec 2014

Our estimated incidence of SADS in m.3243A>G = 2.4 per 1000 person-years

* Incidence of sudden unexpected death in population of <=35yo is 1 to 3.73 / 100,000

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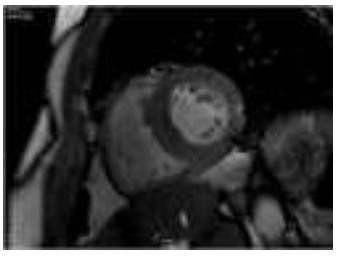
What should we do?



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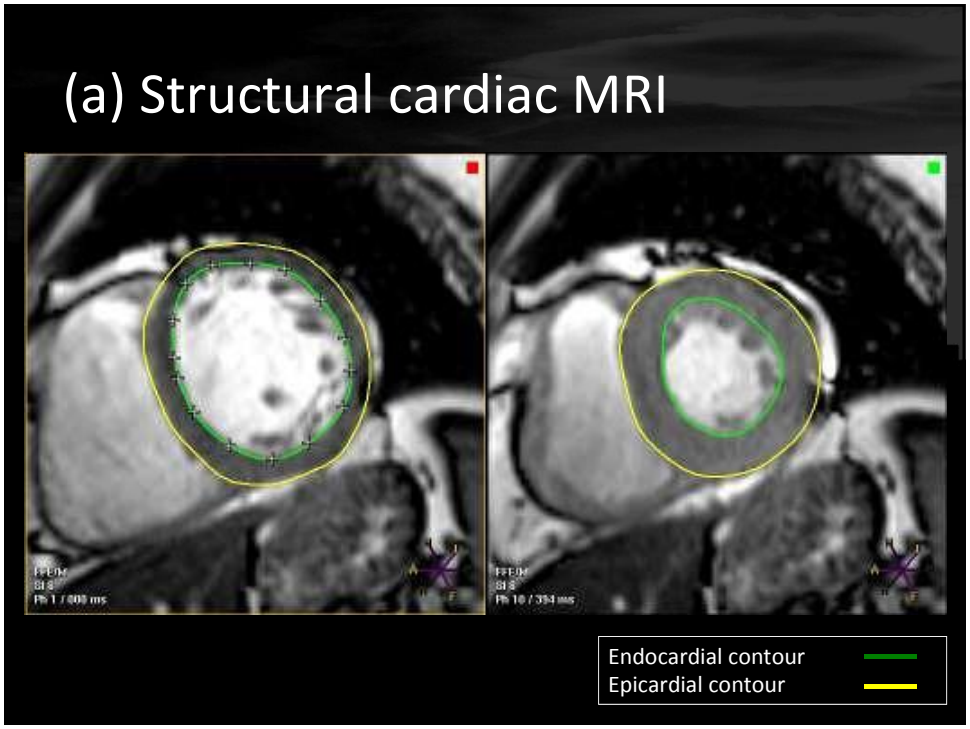

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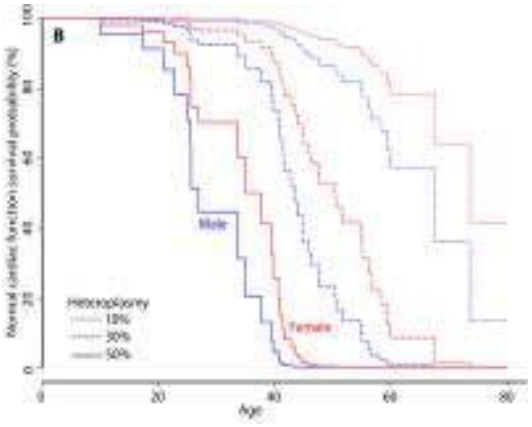
Predictors of Cardiomyopathy in m.3243A>G



Acknowledgement: J Grady

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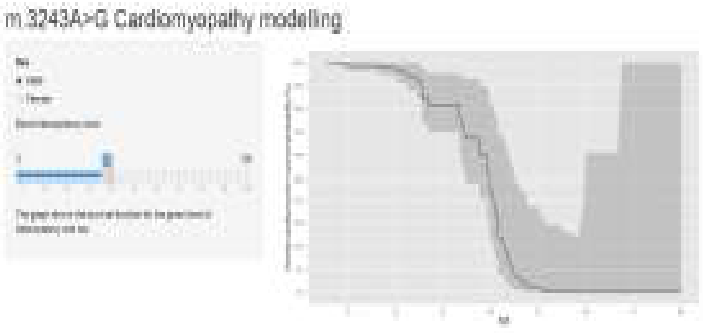
http://research.ncl.ac.uk/mitoresearch/cardio/



* Both blood and urine heteroplasmies are predictor for cardiomyopathy but blood is better.

Together with J Grady and G Gorman

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Cardiac and Cases 2

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Case : Back to basics

- 30 year old woman
- 6 years ago presented with intermittent episodes of
  - Ocassional twitches when tired
  - 'off balance'
  - palpatations
- Familial screening: optic atrophy

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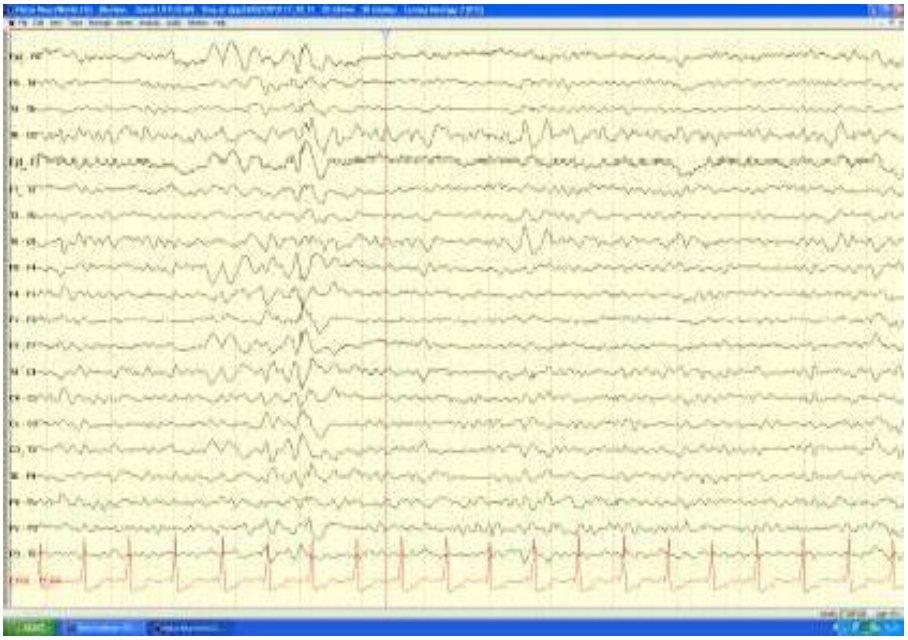

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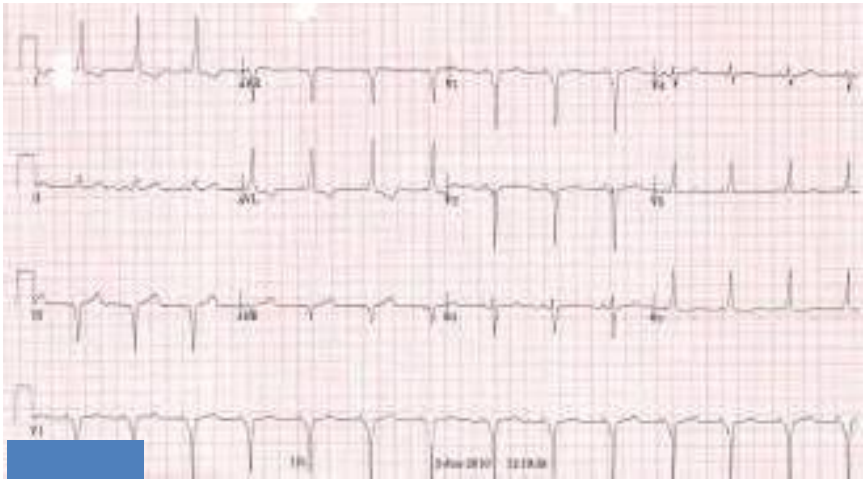

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Diagnoses:

- Myoclonus
- WPW- ablation therapy not required
- Developed lipomas on nap of neck and submandibular region (2007-2008)
- MERRF (8344A>G)

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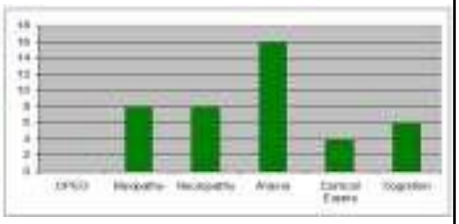
8344A>G
(MERRF)



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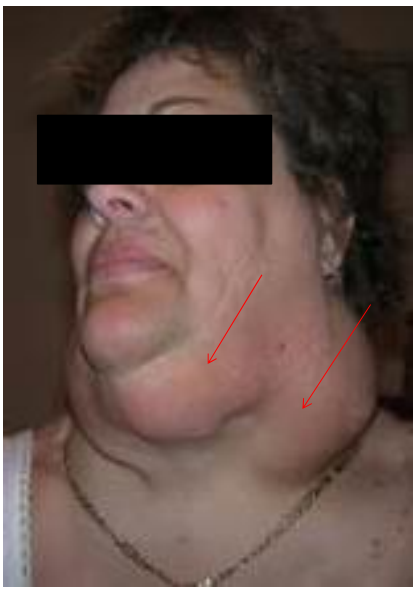
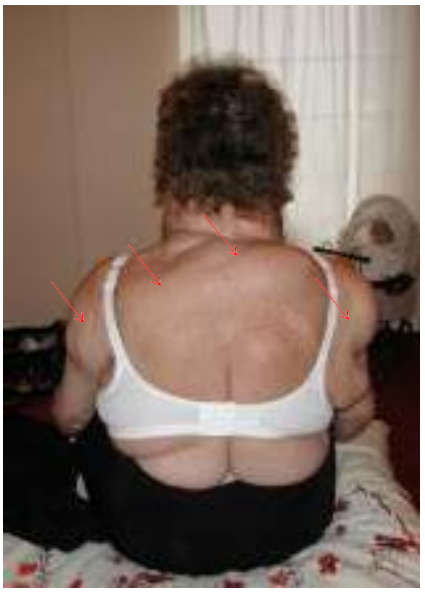
m.8344 A>G and lipomas





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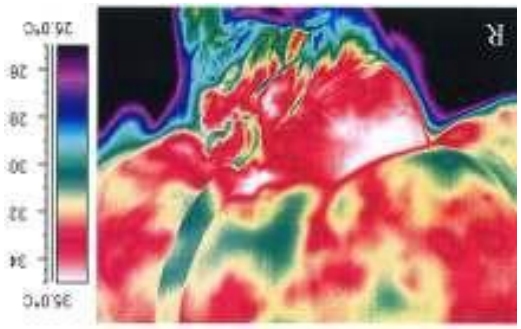
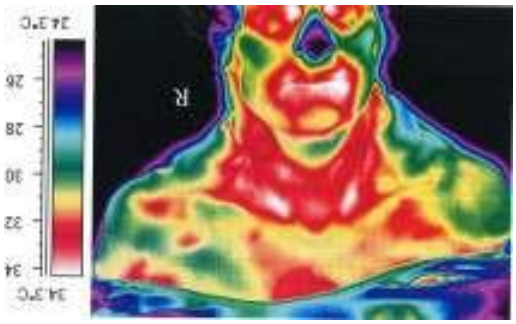


Patient 3-dorsal



Patient 2-ventral

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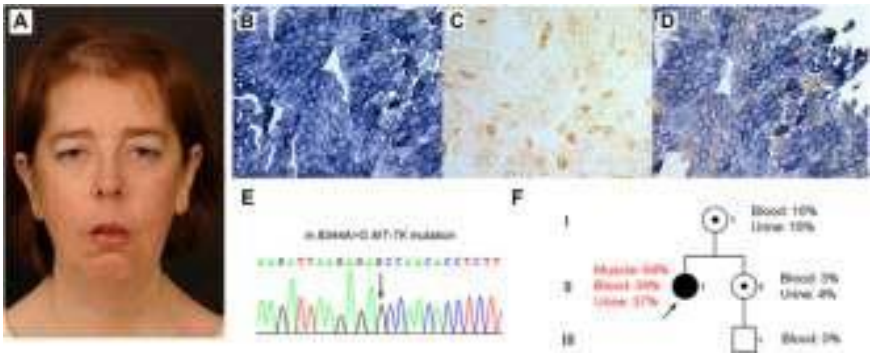
Distal weakness with respiratory insufficiency (MERRF)



(A) Clinical features include hair thinning, bilateral ptosis, and marked facial diplegia with prominent temporalis muscle wasting, jaw weakness and mild neck flexor and extension weakness. (B) Illustrates a severe mitochondrial histochemical defect, characterized by subsarcolemmal mitochondrial accumulation (ragged-red fibers) on the SDH reaction and in excess of 90% COX-deficient fibers following COX (C) and sequential COX-SDH (D) histochemistry. (E) Sequencing of the mitochondrial genome identified the well-characterised m.8344A > G MTTK gene mutation (94% mutation load, muscle) but lower levels in blood and urine by quantitative pyrosequencing. (F) Maternal inheritance.

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GIT and pseudo-obstruction

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m.3243A>G *MTTL1*

Poor weight gain **Short stature**

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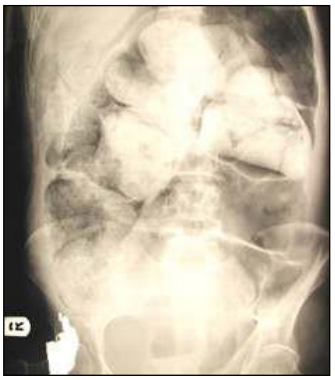
Bowel Dysmotility with m.3243A>G

PEG tube feeding



AXR may show bowel obstruction and faecal loading

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Evolution of pseudo-obstruction

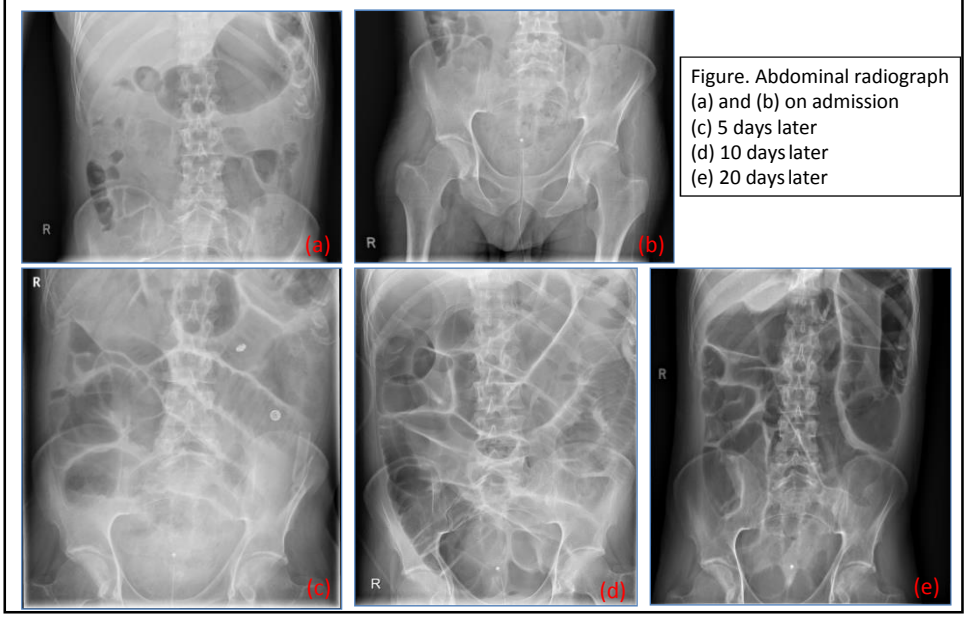

Figure. Abdominal radiograph
(a) and (b) on admission
(c) 5 days later
(d) 10 days later
(e) 20 days later

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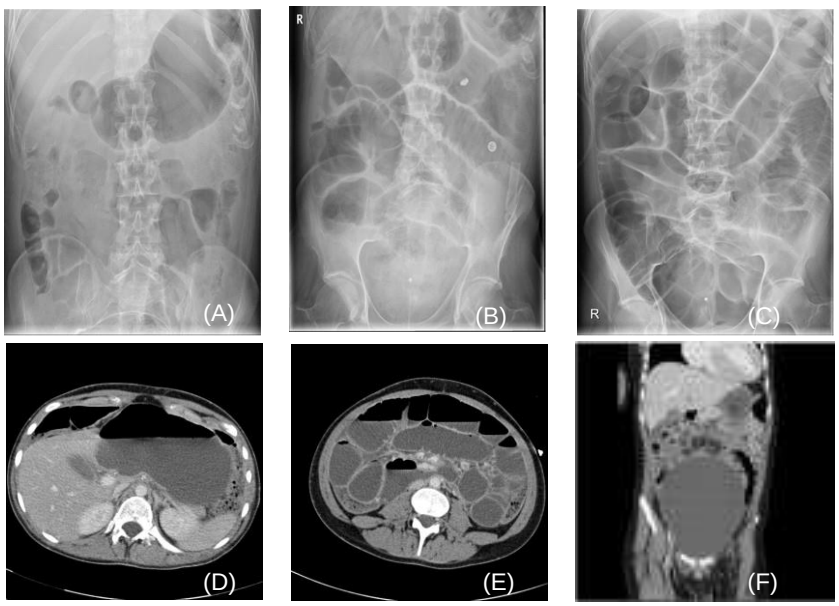

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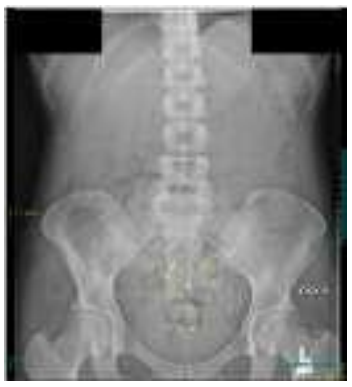

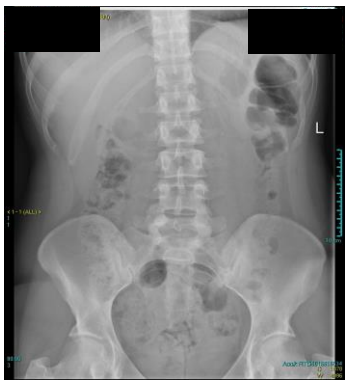

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Best Practice Guidelines

http://www.newcastle-mitochondria.com

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Pattern Recognition











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Thank you

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