5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 1

Mitochondrial diseases for beginners (Level 1)

Diagnostic approach: which are the red flags?

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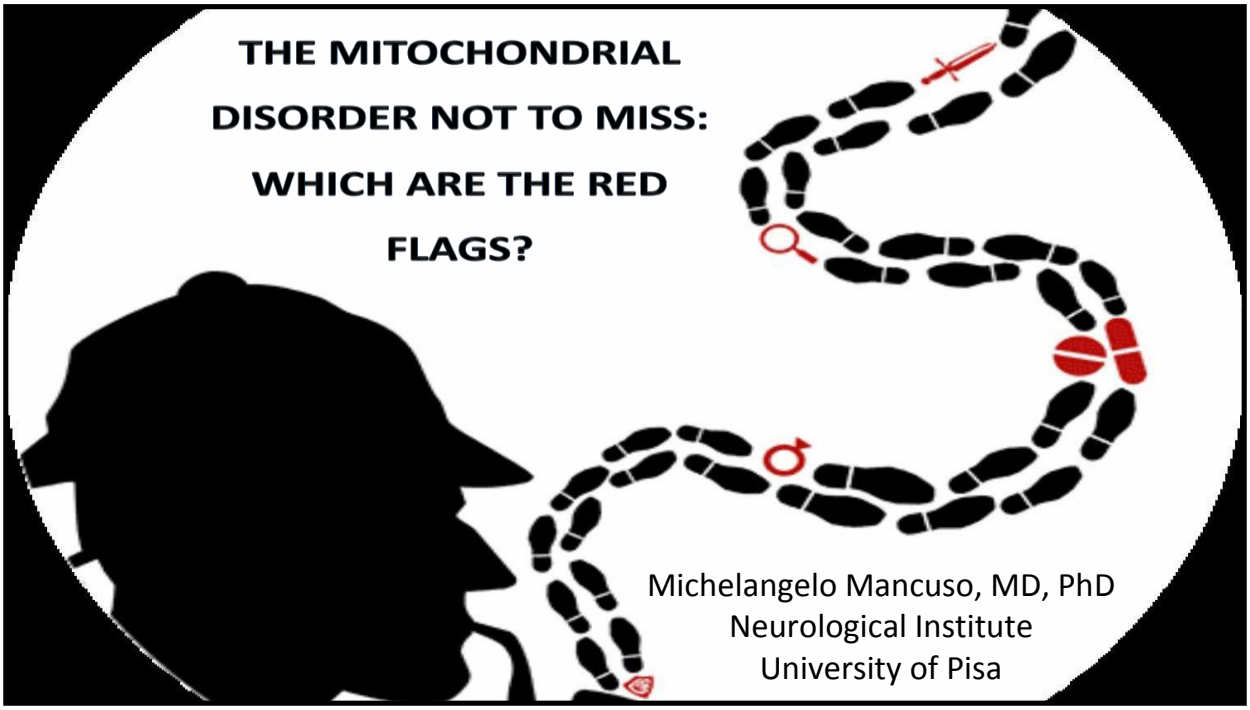

1

NOTHING TO DISCLOSE

2

Mitochondrial disorders in neurology are either **underdiagnosed**

"what is this bizarre syndrome?"

or **overdiagnosed**

"this syndrome is so bizarre that it must be mitochondrial"

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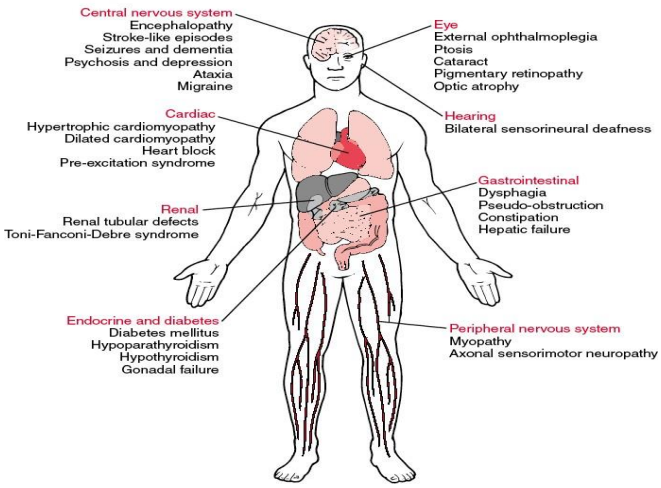
MITOCHONDRIAL DISORDERS



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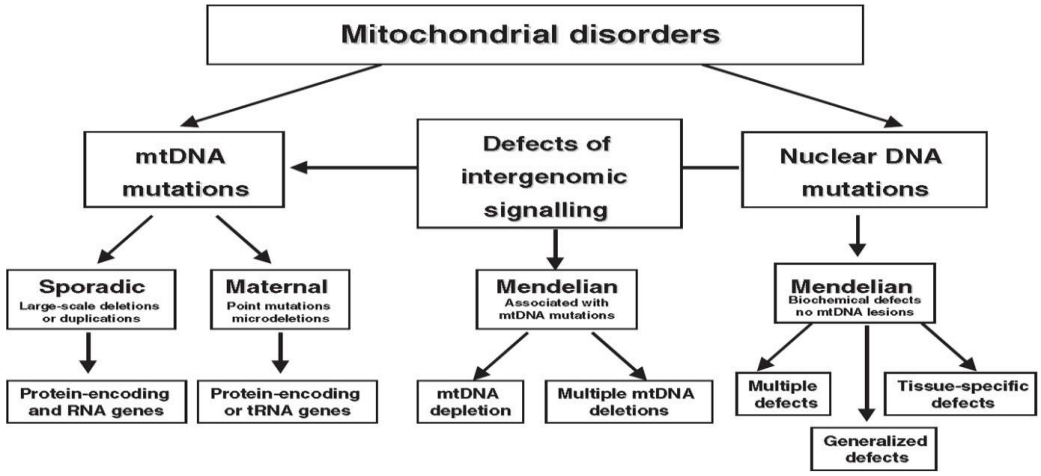

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The **same** genetic defect may result in **different** phenotypes in different individuals or families (intra-and inter- familiar clinical heterogeneity) and, **vice versa**, homogeneous phenotypes may be expression of different mutations.

Some nosological **well defined syndromes** are often associated with specific mutations.

However, in most cases, **phenotypes are heterogeneous** and polymorphous, and may range from pure myopathy to multisystemic disorders, making it difficult to establish a precise genotype/phenotype correlation

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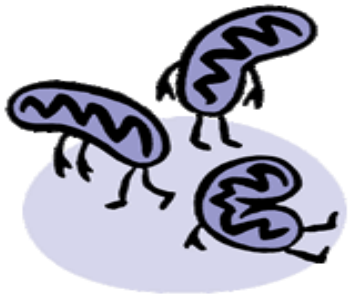
In fact…

- 100s of different mtDNA-related diseases
- 100s of different nDNA-related diseases
- Even in individuals with the same mutation, there are different symptoms
- Change over time
- Challenging to diagnose
- Challenging to treat



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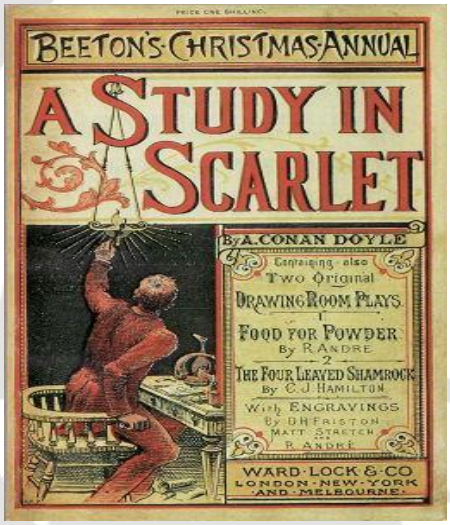

There's the scarlet thread of murder running through the colourless skein of life, and our duty is to unravel it, and isolate it, and expose every inch of it

A Study in Scarlet, 1887
Arthur Conan Doyle

There's the scarlet thread of **mitochondria** running through the colourless skein of life, and our duty is to unravel it, and isolate it, and expose every inch of it

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Diagnostic approach

The diagnostic process **is no different from that employed for other diseases** and includes patient and family history, physical and neurologic examination, routine and special laboratory tests, exercise physiology, muscle biopsy for morphology and biochemistry, and molecular genetic screening

You see Watson, but you do not observe

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Diagnosis: assessing involvement

- Brain MRI (also spectroscopy)
- EEG
- Sleep Study
- Echocardiogram
- EKG
- Abdominal Ultrasound
- Swallow Evaluation
- Nutrition Assessment
- Developmental Assessment
- Vision Test
- Ophthalmologic Examination+OCT
- Hearing Test

- Labs:
  - Liver Function Tests
  - Fasting Serum Glucose
  - Ammonia
  - Amino Acids
  - Lactic Acid
  - Free/Total Carnitine
  - Urine organic aciduria
  - Biomarkers

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Family history

A family history must be taken meticulously, with special attention to minimal and **apparently unspecific** signs in the maternal lineage, including short stature, diabetes, migraine, hearing loss, exercise intolerance and psychiatric disorders

The little things are infinitely the most important

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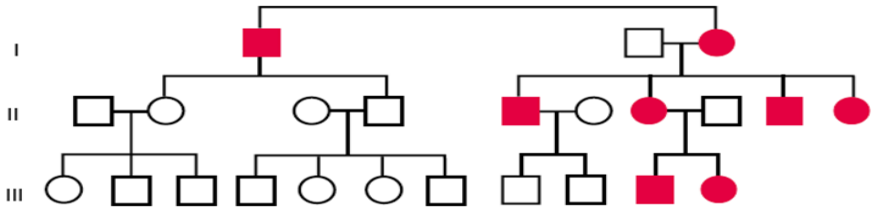
Maternal vs Mendelian inheritance

Maternal inheritance of a clinical disorder is indicative of a mtDNA-related disease;

however, very low levels of heteroplasmy may not cause a full phenotype, possibly causing only mild or subclinical signs.



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Maternal vs Mendelian inheritance

Mendelian inheritance is also very common in mitochondrial diseases because of the multiple nuclear genes causing disease. Parental consanguinity suggests autosomal recessive inheritance. Incomplete penetrance, and absence of genotype-phenotype correlation, including those within the same family, is common.

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Neurotherapeutics (2013) 10:243–250
DOI 10.1007/s13311-012-0173-2

REVIEW

Genetic Counseling in Mitochondrial Disease

Jodie M. Vento · Belen Pappa

The little things are infinitely the most important

AS A GENERAL ROLE, mtDNA SINGLE DELETION IS ALWAYS SPORADIC!

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Onset and progression

Age at onset is not a red flag of mitochondriopathy.

- Onset varies widely in mtDNA and nuclear DNA-related diseases, even within members of the same family.
- Specific mitochondrial syndromes have onset in infancy or early childhood and may follow several months of normal development (i.e. mitochondrial depletion or Leigh syndromes, revised in Ardissone et al, 2014).
- Vice versa, very late onset is frequent in disorders of intergenomic communications caused by *POLG* mutation or other nuclear genes.

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Onset and progression

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Table 5 Pediatric presentations of mitochondrial disease by age of symptom onset

Antenatal	Intra-uterine growth retardation, birth anomalies (20 %): poly-/oligohydramnios, arthrogryposis, ventricular septal defect, hypertrophic cardiomyopathy, VACTERL (vertebral and limb defects)
Neonates	Keto/lactic acidotic coma: apnea, seizures, severe hypotonia; hepatomegaly or hepatic failure; severe sideroblastic anemia; concentric hypertrophic cardiomyopathy; proximal tubulopathy (Fanconi syndrome); myopathy
Infants	Failure to thrive, chronic diarrhea, recurrent acute myoglobinuria, proximal tubulopathy, nephrotic syndrome, liver failure, Leigh syndrome
Childhood	Multisystemic disease, brain (seizure, regression, dystonia, ataxia, encephalopathy, stroke-like episodes), progressive myopathy, myalgia, exercise intolerance; hypertrophic or dilated cardiomyopathy, heart block; multiple endocrinopathies, CPEO/ptosis, retinopathy, cataracts, Sensorineural hearing loss

VACTERL = OMIM#192350 (also known as VATER): vertebral defects (V), anal atresia (A), cardiac malformations (C), tracheoesophageal fistula with esophageal atresia (TE), and radial or renal dysplasia R), limb anomalies (L)

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Onset and progression

Age at onset is not a red flag of mitochondriopathy.

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- Vice versa, very late onset is frequent in disorders of intergenomic communications caused by

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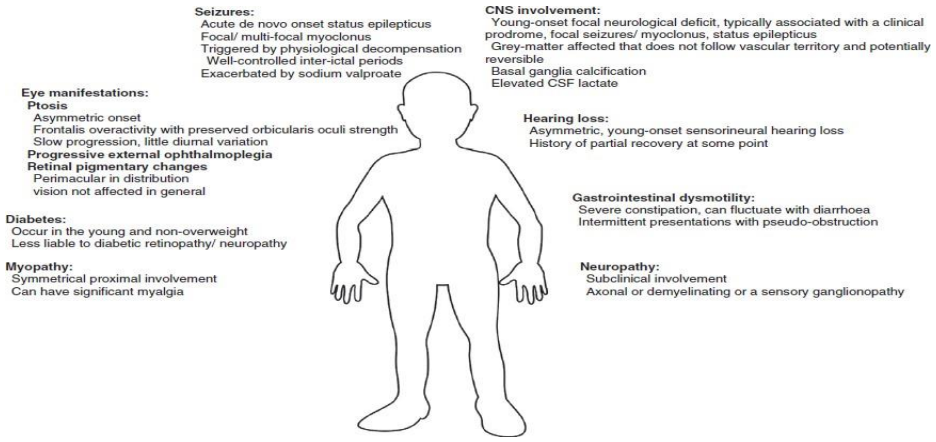
Clinical symptoms and signs



As a general hint, **the apparently unrelated involvement of two or more tissues** should suggest the possibility of mitochondrial disease, including the cases where the family history is unremarkable

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Symptom Review: brain

- Seizures
- Myoclonus
- Ataxia
- Hypotonia
- Spasticity
- Dystonia
- Tremor
- Parkinsonism
- Other movement disorder
- "stroke-like" episodes
- Migraine
- Central Apnea
- Developmental Delays
- Developmental Regression
- Dementia
- Learning Disabilities
- Autism or autistic-like features
- Behavioral Concerns
- Psychiatric Conditions
- Coma

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Central Nervous System:

Table 6 Red flag symptoms related to primary mitochondrial disease

Symptom	Red flag signs
Stroke	Located in a nonvascular distribution
Basal ganglia lesions	Bilateral symmetric (characteristic of Leigh syndrome); also with brainstem lesions
Encephalopathy–hepatopathy	Precipitated by valproic acid exposure; associated hepatic failure
Epilepsy	Epilepsia partialis continua, myoclonus, status epilepticus
Cognitive decline	Regression with illness
Ataxia	Associated with epilepsy or other systemic symptoms; neuroimaging may show cerebellar atrophy, white matter lesions, basal ganglia lesion
Ocular signs	Optic nerve atrophy, ophthalmoplegia, ptosis; retinopathy
Sensorineural hearing loss	At early age, accompanied by other systemic symptoms
Cardiac conduction disorders	Wolff–Parkinson–White, heart block
Cardiomyopathy	Accompanied by skeletal myopathy
Glomerulopathy	Steroid-resistant nephropathy
Proximal tubulopathy; Fanconi's syndrome	Renal tubular acidosis; tubulointerstitial nephritis
Pancreatic dysfunction	Diabetes mellitus
Thyroid dysfunction	Hypothyroidism
Gastrointestinal dysmotility	Chronic intestinal pseudo-obstruction
Hepatopathy	With encephalopathy

…but also myoclonus, psychomotor retardation or regression, migraine, tremor and parkinsonism.

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CHALLENGES OF MODERN MITOCHONDRIAL MEDICINE

- INTERNATIONAL COLLABORATIONS
- STAKEHOLDERS SHARING KNOWLEDGE
- PATIENTS REGISTRIES
- HPO LANGUAGE
- THE GLOBAL REGISTRY CHALLENGE

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"Construction of a database for a nation-wide Italian collaborative network of mitochondrial diseases"

The Italian Network of Mitochondrial Diseases

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Italian Network of Mitochondrial Diseases

www.mitochondrialdisease.it

1800 Patients

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J Neurol
DOI 10.1007/s00415-015-7710-y

ORIGINAL COMMUNICATION

Redefining phenotypes associated with mitochondrial DNA single deletion

Michelangelo Mancuso[1] · Daniele Orsucci[1] · Corrado Angelini[2] · Enrico Bertini[3] · Valerio Carelli[4] · Giacomo Pietro Comi[5] · Maria Alice Donati[6] · Antonio Federico[7] · Carlo Minetti[8] · Maurizio Moggio[9] · Tiziana Mongini[10] · Filippo Maria Santorelli[11] · Serenella Servidei[12] · Paola Tonin[13] · Antonio Toscano[14] · Claudio Bruno[8] · Luca Bello[2] · Elena Caldarazzo Ienco[1] · Elena Cardaioli[7] · Michela Catteruccia[3] · Paola Da Pozzo[7] · Massimiliano Filosto[17] · Costanza Lamperti[16] · Isabella Moroni[15] · Olimpia Musumeci[14] · Elena Pegoraro[2] · Dario Ronchi[5] · Donato Sauchelli[12] · Mauro Scarpelli[13] · Monica Sciacco[9] · Maria Lucia Valentino[4] · Liliana Vercelli[10] · Massimo Zeviani[16] · Gabriele Siciliano[1]

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Available online at www.sciencedirect.com
SciVerse ScienceDirect
Neuromuscular Disorders 22 (2012) 577–586
www.elsevier.com/locate/nmd

Review

Single deletions in mitochondrial DNA – Molecular mechanisms and disease phenotypes in clinical practice

R.D.S. Pitceathly [a], S. Rahman [a,b,c], M.G. Hanna [a,d,*]

[a] MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK
[b] Mitochondrial Research Group, Clinical and Molecular Genetics Unit, UCL Institute of Child Health, London WC1N 1EH, UK
[c] Metabolic Unit, Great Ormond Street Hospital for Children, London WC1N 3JH, UK
[d] Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK

Three well-defined phenotypes

5. Clinical phenotypes associated with single mitochondrial DNA deletions

5.1. Pearson marrow-pancreas syndrome

5.2. Kearns–Sayre syndrome (KSS)

5.3. Progressive external ophthalmoplegia (PEO)

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RESULTS: Kearns-Sayre syndrome (KSS)

Progressive external ophthalmoplegia plus:

- **pigmentary retinopathy**
- onset before age 20

Plus at least one of:

- cerebellar ataxia
- cardiac conduction block
- CSF protein > 0.1 g/L

Neuromuscular Disorders 22 (2012)
Single deletions in mitochondrial DNA – Molecular mechanisms and disease phenotypes in clinical practice
R.D.S. Pitceathly [a], S. Rahman [a,b,c], M.G. Hanna [a,d,*]

With these criteria: 15 subjects with KSS (6.6%)

M/F 0.88, age at onset 9.4 ± 4.8 years,

last control 29.4 ± 18.0 years, died 2/15 (13.3%)

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	Retinopathy $N = 24$	Non-retinopathy $N = 204$	P
Hearing loss	14 (58.3 %)	28 (13.7 %)	0.000004
Ataxia	13 (54.2 %)	15 (7.4 %)	<0.000001
Failure to thrive/short st.	7 (29.2 %)	15 (7.4 %)	0.0035
Diabetes	3 (12.5 %)	17 (8.3 %)	ns
Cardiac conduction def.	4 (16.7 %)	8 (3.9 %)	ns
Increased liver enzymes	1 (4.2 %)	11 (5.4 %)	ns
Anemia	2 (8.3 %)	9 (4.4 %)	ns
Neuropathy	3 (12.5 %)	7 (3.4 %)	ns
Migraine	1 (4.2 %)	9 (4.4 %)	ns
Cognitive involvement	3 (12.5 %)	5 (2.5 %)	ns
Tremor	1 (4.2 %)	6 (2.9 %)	ns
Psychiatric involvement	1 (4.2 %)	6 (2.9 %)	ns
Cardiomyopathy	– (0 %)	6 (2.9 %)	ns
Hypothyroidism	– (0 %)	6 (2.9 %)	ns

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Table 3 Multisystem clinical features associated with ataxia

	Ataxia $N = 28$	Non-ataxia $N = 200$	P
Hearing loss	16 (57.1 %)	26 (13.0 %)	0.000001
Retinopathy	13 (46.4 %)	11 (5.5 %)	<0.000001
Failure to thrive/short st.	14 (50.0 %)	8 (4.0 %)	<0.000001
Diabetes	5 (17.9 %)	15 (7.5 %)	ns
Cardiac conduction def.	2 (7.1 %)	10 (5.0 %)	ns
Increased liver enzymes	3 (10.7 %)	9 (4.5 %)	ns
Anemia	4 (14.3 %)	7 (3.5 %)	ns
Neuropathy	3 (10.7 %)	7 (3.5 %)	ns
Migraine	3 (10.7 %)	7 (3.5 %)	ns
Cognitive involvement	6 (21.4 %)	2 (1.0 %)	0.000048
Tremor	5 (17.9 %)	2 (1.0 %)	0.00035
Psychiatric involvement	3 (10.7 %)	4 (2.0 %)	ns
Cardiomyopathy	1 (3.6 %)	5 (2.5 %)	ns
Hypothyroidism	1 (3.6 %)	5 (2.5 %)	ns

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Table 6 New criteria defining KSS spectrum and PEO in patients with single deletion

KSS spectrum
Ptosis and/or ophthalmoparesis due to an mtDNA single large-scale deletion and at least one of the following features
Retinopathy
Ataxia
Cardiac conduction defects
Hearing loss
Failure to thrive/short stature
Cognitive involvement
Tremor
Cardiomyopathy
PEO
Ptosis and/or ophthalmoparesis due to a mtDNA single large-scale deletion not fulfilling the new "KSS spectrum" criteria or criteria for Pearson syndrome

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With the new clinical definition, we were able to classify almost all (97%) our single-deletion patients:

- 62.7% PEO (141/22), vs 54.6 NMD 2012
- 31.6% KSS (71/225), vs 6.6 NMD 2012
- 2.7% Pearson (6/225), NMD 2.7

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"New" KSS: multisystem involvement, more severe muscular impairment (weakness and wasting), MRI frequently abnormal (white matter, brainstem, basal nuclei), mean age at onset 21 years, worst prognosis.

"New" single-deletion PEO: prominent myopathic involvement, MRI frequently normal, mean age at onset 27 years, better prognosis.

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J Neurol
DOI 10.1007/s00415-013-7225-3

ORIGINAL COMMUNICATION

The m.3243A>G mitochondrial DNA mutation and related phenotypes. A matter of gender?

Michelangelo Mancuso · Daniele Orsucci · Corrado Angelini · Enrico Bertini · Valerio Carelli · Giacomo Pietro Comi · Alice Donati · Carlo Minetti · Maurizio Moggio · Tiziana Mongini · Serenella Servidei · Paola Tonin · Antonio Toscano · Graziella Uziel · Claudio Bruno · Elena Caldarazzo Ienco · Massimiliano Filosto · Costanza Lamperti · Michela Catteruccia · Isabella Moroni · Olimpia Musumeci · Elena Pegoraro · Dario Ronchi · Filippo Maria Santorelli · Donato Sauchelli · Mauro Scarpelli · Monica Sciacco · Maria Lucia Valentino · Liliana Vercelli · Massimo Zeviani · Gabriele Siciliano

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Clinical features of the A3243G carriers (n = 111).

	Onset 24.5 ± 15.7 years*	Last evaluation 39.9 ± 18.7 years
Hearing loss	37 (33.3%)	68 (61.3%)
Generalized seizures	21 (18.9%)	43 (38.7%)
Diabetes	20 (18.0%)	47 (42.3%)
Ptosis/ophthalmoparesis	15 (13.5%)	33 (29.7%)
Stroke-like episodes	14 (12.6%)	48 (43.2%)
Migraine	14 (12.6%)	29 (26.1%)
Exercise intolerance	14 (12.6%)	36 (32.4%)
Muscle weakness	12 (10.8%)	41 (36.9%)
Heart disease	10 (9.0%)	34 (30.6%)
Cognitive involvement	10 (9.0%)	27 (24.3%)
Failure to thrive/short st.	8 (7.2%)	16 (14.4%)
Increased CK	7 (6.3%)	21 (18.9%)
Muscle pain	7 (6.3%)	13 (11.7%)
Muscle wasting	5 (4.5%)	22 (19.8%)
Vomiting	5 (4.5%)	6 (5.4%)
Gastrointestinal dysmotil.	4 (3.6%)	15 (13.5%)
Neuropathy	4 (3.6%)	12 (10.8%)
Ataxia	3 (2.7%)	24 (21.6%)
Myoclonus	3 (2.7%)	6 (5.4%)
Hypothyroidism	2 (1.8%)	5 (4.5%)
Hypotonia	2 (1.8%)	13 (11.7%)
Retinopathy	2 (1.8%)	11 (9.9%)
Psychiatric involvement	1 (0.9%)	6 (5.4%)
Optic neuropathy	1 (0.9%)	5 (4.5%)
Hypogonadism	1 (0.9%)	5 (4.5%)
Pyramidal signs	-	14 (12.6%)
Status epilepticus	-	5 (4.5%)
Respiratory impairment	-	4 (3.6%)

Swallowing impairment, tremor, anemia, cataract, dyskinesia, hepatopathy, kidney inv. < 3%
*[*for the symptomatic patients]*

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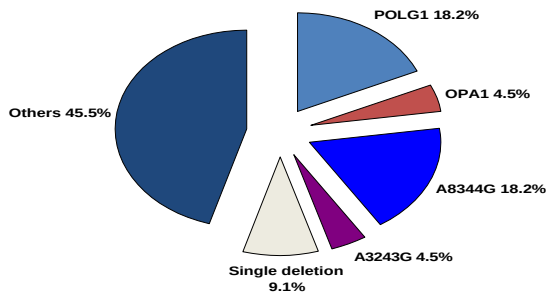
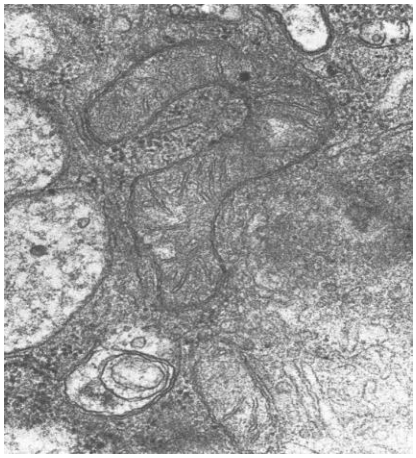
Mitochondrial ataxias (15.9%)

Data from the Italian network of MD





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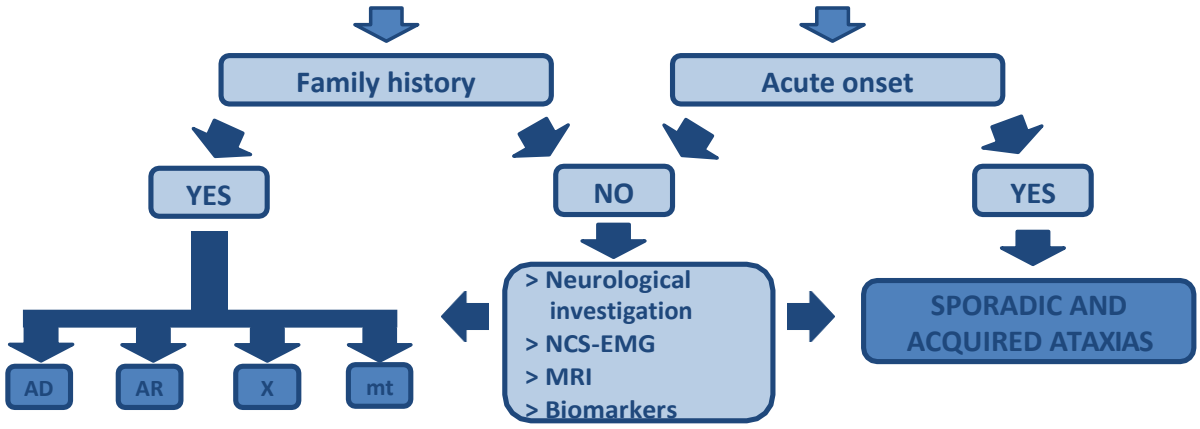
Sporadic and acquired ataxias *versus* genetically confirmed



AD, autosomal dominant; **AR**, autosomal recessive; **X**, X-linked; **mt**, mitochondrial
NCS-EMG, nerve conduction studies-electromyogram; **MRI**, magnetic resonance imaging

Mancuso et al, 2014

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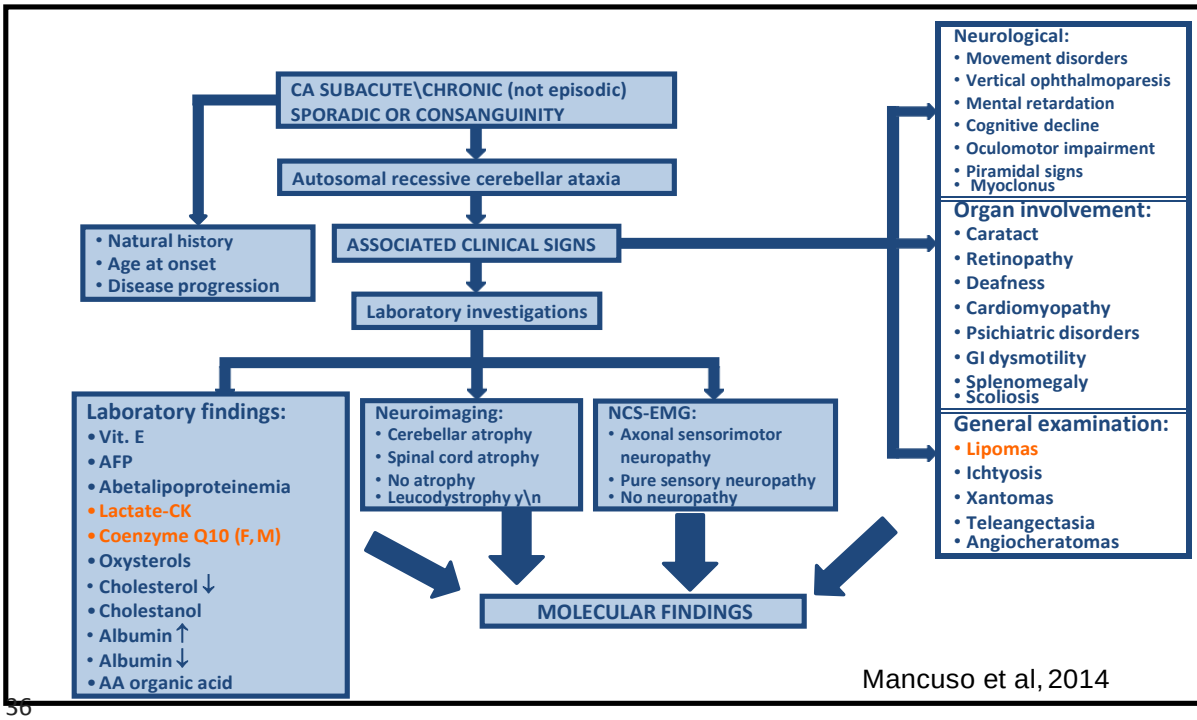

Mancuso et al, 2014

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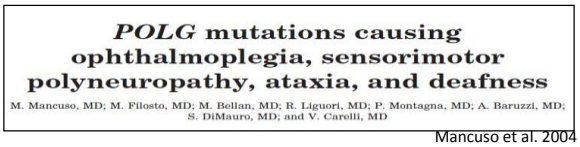
MITOCHONDRIAL ATAXIAS – SANDO



***POLG* mutations causing ophthalmoplegia, sensorimotor polyneuropathy, ataxia, and deafness**

M. Mancuso, MD; M. Filosto, MD; M. Bellan, MD; R. Liguori, MD; P. Montagna, MD; A. Baruzzi, MD; S. DiMauro, MD; and V. Carelli, MD

Mancuso et al. 2004

- Caused by mutations in mitochondrial POLG gene
- POLG encodes the catalytic subunit of mitochondrial DNA polymerase
- Adult-onset disease (typically between 16–40 years of age)
- Typical clinical symptoms include:
  - Sensory ataxic neuropathy
  - Dysarthria
  - Chronic progressive external ophthalmoplegia

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MITOCHONDRIAL ATAXIAS – MIRAS

- Caused by homozygous or compound heterozygous mutations in the POLG1 gene
- Cerebellar ataxia
- Commonly associated with:
  - Mild cognitive impairment
  - Psychiatric abnormalities
  - Involuntary movements
  - Seizures
  - PNP
- Patients may be prone to adverse reactions to valproate manifesting as acute liver failure

MIRAS, mitochondrial recessive ataxia syndrome

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NEUROLOGICAL REVIEW

Heterogeneity of Coenzyme Q_{10} Deficiency

Patient Study and Literature Review

Valentina Emmanuele, MD; Luis C. López, PhD; Andres Berardo, MD; Ali Naini, PhD; Saba Tadesse, BS; Bing Wen, MD; Erin D'Agostino, BA; Martha Solomon, BA; Salvatore DiMauro, MD; Catarina Quinzii, MD; Michio Hirano, MD

Table 3. Clinical Response to CoQ_{10} Supplementation in Major Forms of CoQ_{10} Deficiency

Syndrome (No. of Patients)	CoQ_{10} Doses; Duration	Response to Therapy
Encephalomyopathy (4)	150 mg/d; 3-8 mo	Improvement of muscle symptoms in 4/4 and encephalopathy in 1 patient
Isolated myopathy (8)	150-500 mg/d; 4-12 mo	Improvement in 6 patients
Isolated nephropathy (4)	30 mg/kg/d-100 mg/d; 2-50 mo	Reduced proteinuria in 3 patients; hearing improvement in 1/2 patients; no follow-up data in 1 patient
Infantile multisystemic disease (4)	30 mg/kg/d-300 mg/d; 5-36 mo	Improvement of myopathic symptoms and stabilization of encephalopathy in 1 patient; neurological, but not renal improvement in 1 patient
Cerebellar ataxia (54)	5 mg/kg/d-3000 mg/d; 1 mo-12 y	Improvement of muscle symptoms in 13/20 patients; seizures in 3/14 patients; ataxia in 25/54 patients.

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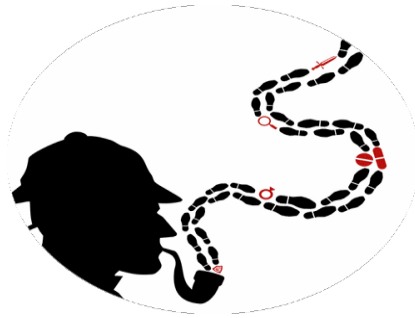
Even though **myoclonus** is not a frequent sign of mitochondriopathy, in a myoclonic patient evidences of mitochondrial dysfunction must be searched, especially if myoclonus is associated with cerebellar **ataxia** (Mancuso et al, 2014).



RESEARCH ARTICLE

Myoclonus in Mitochondrial Disorders

Michelangelo Mancuso, MD, PhD,[1]* Daniele Orsucci, MD,[1] Corrado Angelini, MD,[2] Enrico Bertini, MD, PhD,[3] Michela Catteruccia, MD,[3] Elena Pegoraro, MD, PhD,[2] Valerio Carelli, MD, PhD,[4] Maria L. Valentino, MD,[4] Giacomo P. Comi, MD, PhD,[5] Carlo Minetti, MD,[6] Claudio Bruno, MD, PhD,[6] Maurizio Moggio, MD, PhD,[7] Elena Caldarazzo Ienco, MD,[1] Tiziana Mongini, MD,[8] Liliana Vercelli, MD, PhD,[8] Guido Primiano, MD,[9] Serenella Servidei, MD, PhD,[9] Paola Tonin, MD, PhD,[10] Mauro Scarpelli, MD,[10] Antonio Toscano, MD, PhD,[11] Olimpia Musumeci, MD,[11] Isabella Moroni, MD,[12] Graziella Uziel, MD, PhD,[12] Filippo M. Santorelli, MD,[13] Claudia Nesti, PhD,[13] Massimiliano Filosto, MD, PhD,[14] Costanza Lamperti, MD,[15] Massimo Zeviani, MD, PhD,[16] and Gabriele Siciliano, MD, PhD[1]

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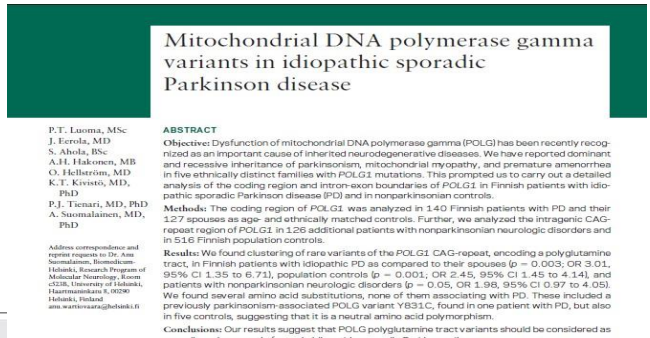
In the last years, a special interest in the "**mitochondrial movement disorders**" has been developed

Parkinsonism with or without muscular signs is a common manifestation of intergenomic communications, i.e. mutations in POLG or Twinkle, and OPA1



Mitochondrial DNA polymerase gamma variants in idiopathic sporadic Parkinson disease

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ABSTRACT

Objective: Dysfunction of mitochondrial DNA polymerase gamma (POLG) has been recently recognized as an important cause of inherited neurodegenerative diseases. We have reported dominant and recessive inheritance of parkinsonism, mitochondrial myopathy, and premature amenorrhea in five ethnically distinct families with *POLG1* mutations. This prompted us to carry out a detailed analysis of the coding region and intron-exon boundaries of *POLG1* in Finnish patients with idiopathic sporadic Parkinson disease (PD) and in nonparkinsonian controls.

Methods: The coding region of *POLG1* was analyzed in 140 Finnish patients with PD and their 127 spouses as age- and ethnically matched controls. Further, we analyzed the intragenic CAG-repeat region of *POLG1* in 126 additional patients with nonparkinsonian neurologic disorders and in 516 Finnish population controls.

Results: We found clustering of rare variants of the *POLG1* CAG-repeat, encoding a polyglutamine tract, in Finnish patients with idiopathic PD as compared to their spouses ($p = 0.003$; OR 3.01, 95% CI 1.35 to 6.71), population controls ($p = 0.001$; OR 2.45, 95% CI 1.45 to 4.14), and patients with nonparkinsonian neurologic disorders ($p = 0.05$, OR 1.98, 95% CI 0.97 to 4.05). We found several amino acid substitutions, none of them associating with PD. These included a previously parkinsonism-associated POLG variant Y831C, found in one patient with PD, but also in five controls, suggesting that it is a neutral amino acid polymorphism.

Conclusions: Our results suggest that POLG polyglutamine tract variants should be considered as a predisposing genetic factor in idiopathic sporadic Parkinson disease.

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Neuroscience Letters 556 (2013) 1–4

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Twinkle mutation in an Italian family with external progressive ophthalmoplegia and parkinsonism: A case report and an update on the state of art

Lorenzo Kiferle*, Daniele Orsucci, Michelangelo Mancuso, Annalisa Lo Gerfo, Lucia Petrozzi, Gabriele Siciliano, Roberto Ceravolo, Ubaldo Bonuccelli

Section of Neurology, Department of Clinical and Pathological Medicine, University of Pisa, via Roma 67, 56126 Pisa, Italy

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Symptom Review: neuromuscular

	Patients (1330 tot with full phenotype described)	Percentage
Ptosis/ophthalmoparesis	636	47,8
Muscle weakness	488	36,7
Hearing loss	330	24,8
Exercise intolerance	279	21
Optic neuropathy	241	18,1
Muscle wasting	233	17,5
Cerebellar ataxia	198	14,8
Cognitive involvement	189	14,2
Hypotonia	180	13,5
Neuropathy	163	12,2
Swallowing impairment	162	12,1
Epileptic seizures	152	11,4
Muscle pain	152	11,4
Diabetes	121	9
Pyramidal involvement	115	8,6
Respiratory impairment	115	8,6
Cardiomyopathy	106	7,9
Migraine	102	7,6
Retinopathy	92	6,9
Gastroint. dysmotility	69	5,1

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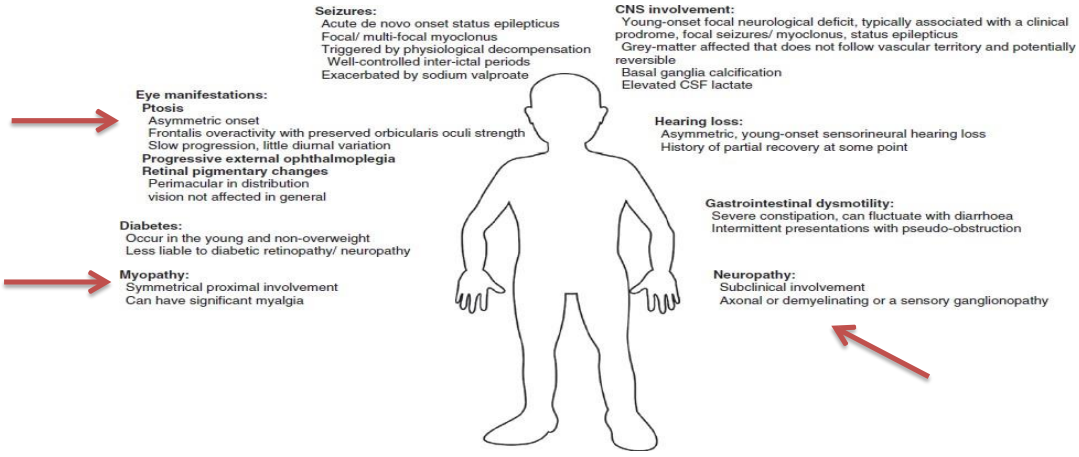
Muscle and nerve

exercise intolerance, weakness, dysphagia, respiratory failure, ptosis, ophtalmoparesis, cramps, muscle wasting and paresthesia



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PRIMARY MITOCHONDRIAL MYOPATHIES

genetically defined disorders leading to defects of oxidative phosphorylation affecting predominantly, but not exclusively, skeletal muscle (see below for methodology). Secondary involvement of mitochondria, frequently observed in multiple neuromuscular diseases (i.e. inclusion body myositis, Duchenne muscular dystrophy, Kennedy disease) are not considered PMM

Workshop report

International Workshop:
Outcome measures and clinical trial readiness in primary mitochondrial myopathies in children and adults. Consensus recommendations.
Rome, Italy, 16–18 November 2016

Michelangelo Mancuso [a,*], Robert McFarland [b], Thomas Klopstock [c], Michio Hirano [d] on behalf of the consortium on Trial Readiness in Mitochondrial Myopathies [†]

[a] Department of Experimental and Clinical Medicine, Neurological Institute, University of Pisa, Italy.
[b] Wellcome Trust Centre for Mitochondrial Research, Institute of Genetic Medicine, Department of Physiology and Functional Genomics NE1 3BZ, Newcastle University, Newcastle upon Tyne, UK
[c] Friedrich-Baur-Institut an der Neurologischen Klinik und Poliklinik, LMU München, Ziemssenstr. 1a, 80336 München, Federal Republic of Germany
[d] Department of Neurology, H. Houston Merritt Neuromuscular Research Center, Columbia University Medical Center, New York, NY, USA

Received 26 June 2017

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PMM: clinical presentation

- Fatigue (defined as an overwhelming sense of tiredness, lack of energy and feeling of exhaustion)
- Exercise Intolerance
- Pain/Myalgia
- Weakness
- Wasting
- Dysphagia
- Spasms
- Myoglobinuria, triggered by exercise (cyt b or CoQ10 deficiency)
- Ptosis
- ophtalmoparesis

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Neuromuscular Disorders 22 (2012) S226–S229

NMD

www.elsevier.com/locate/nmd

Fatigue and exercise intolerance in mitochondrial diseases. Literature revision and experience of the Italian Network of mitochondrial diseases

M. Mancuso [a,*], C. Angelini [b], E. Bertini [c], V. Carelli [d], G.P. Comi [m], C. Minetti [f], M. Moggio [e], T. Mongini [g], S. Servidei [h], P. Tonin [i], A. Toscano [j], G. Uziel [k], M. Zeviani [l], G. Siciliano [a], The Nation-wide Italian Collaborative Network of Mitochondrial Diseases

Genotype-based approach. The patients have been divided in two groups, with and without exercise intolerance. n.s., not significant difference. LHON: Leber hereditary optic neuropathy.

	Exercise intolerance: No (n = 878)	Exercise intolerance: Yes (222)	P
mtDNA A3243G mutation	62 (7.1%)	33 (14.9%)	**<0.0005**
mtDNA A8344G mutation	27 (3.1%)	9 (4.1%)	n.s.
mtDNA T8993C	19 (2.2%)	1 (0.5%)	n.s.
mtDNA LHON mutations	98 (11.2%)	1 (0.5%)	**<0.0001**
OPA1 mutations	85 (9.7%)	1 (0.5%)	**<0.0001**
POLG mutations	33 (3.8%)	8 (3.6%)	n.s.

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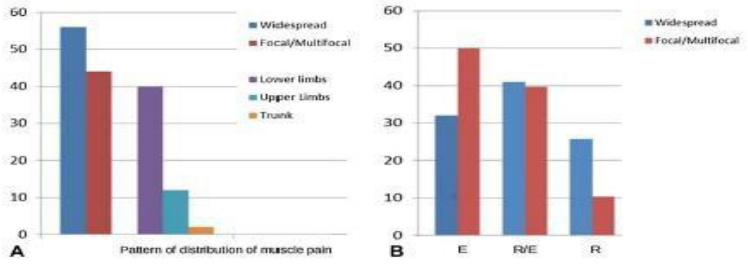
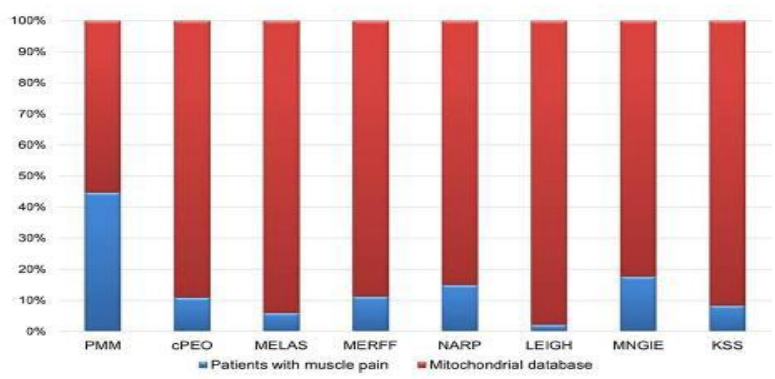
Journal of Neurology
https://doi.org/10.1007/s00415-019-09219-x

ORIGINAL COMMUNICATION

Muscle pain in mitochondrial d network

Massimiliano Filosto[1] · Stefano Cotti Piccinel
Olimpia Musumeci[5] · Paola Tonin[6] · Filippo Mai
Liliana Vercelli[3] · Anna Rubegni[7] · Anna Galvag
Antonio Toscano[5] · Alessandro Padovani[1] · Gab





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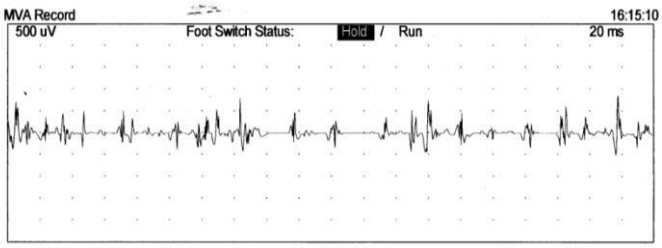
Electromyography (EMG) may identify myopathic motor unit potentials and early recruitment, which are **nonspecific signs of myopathy**, whereas the electrodiagnostic detection of a **subclinical peripheral neuropathy**, when present, would provide a clue for a **more systemic disease** and might indirectly suggest a mitochondrial disease. However, EMG **can also be normal** in mitochondrial myopathy, especially when the myopathy is restricted to the extraocular muscles



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NEUROPATHIES

	Patients (n = 1156)	%
Ptosis/ophthalmoparesis	617	53.4
Muscle weakness	446	38.6
Hearing loss	279	24.1
Exercise intolerance	239	20.7
Optic neuropathy	214	18.5
Muscle wasting	212	18.3
Cerebellar ataxia	186	16.1
Cognitive involvement	180	15.6
Hypotonia	179	15.5
Neuropathy	143	12.4
Swallowing impairment	137	11.9
Epileptic seizures	131	11.3
Muscle pain	124	10.7
Pyramidal involvement	112	9.7
Diabetes	102	8.8

Mean age at onset 24.3 ± 20.1 years

Age at last evaluation 39.8 ± 22.3 years

Childhood onset [before age 16-yrs] 43.1%

Females 52.7%

Mancuso et al 2016

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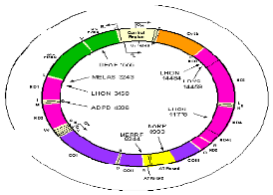
	Neuropathy: No (n = 1013)	Neuropathy: Yes (n = 143)	*P*
mtDNA single deletion	218 (21.5%)	9 (6.3%)	**0.000003**
mtDNA A3243G mutation	90 (8.9%)	12 (8.4%)	n.s.
mtDNA A8344G mutation	30 (3.0%)	5 (3.5%)	n.s.
mtDNA T8993C mutation	12 (1.2%)	6 (4.2%)	n.s.
mtDNA LHON mutations	103 (10.2%)	1 (0.7%)	**0.00002**
Other mtDNA mutations	53 (5.2%)	7 (4.8%)	n.s.
OPA1 mutations	72 (7.1%)	5 (3.5%)	n.s.
POLG mutations	26 (2.6%)	19 (13.3%)	**< 0.000001**
Twinkle mutations	22 (2.2%)	6 (4.2%)	n.s.
SURF1 mutations	10 (1.0%)	10 (7.0%)	**0.00004**
PDHA1 mutations	11 (1.1%)	1 (0.7%)	n.s.
TP mutations	2 (0.2%)	9 (6.3%)	**< 0.000001**

Significance levels after Bonferroni's correction: 0.0042



"Construction of a database for a nation-wide Italian collaborative network of mitochondrial diseases"

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Symptom Review: heart, lungs, kidneys, bladder, endocrine

- Pulmonary:
  - Dyspnea
  - Obstructive Sleep Apnea
- Heart:
  - Cardiomyopathy
  - Arrhythmia
  - Heart Block
- Kidney:
  - Renal Tubular Acidosis
  - Renal Failure
- Hearing loss
- Bladder:
  - Urinary Retention
  - Incomplete Emptying
- Endocrine:
  - Short Stature
  - Diabetes Mellitus (MIDD)
  - Hypothyroidism
  - Hypoparathyroidism
  - Adrenal Insufficiency

MIDD+SNHL: m.3243

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Heart AND mt

- Hypertrophic (HCM):
  - MELAS
- Dilated (DCM):
  - Barth sy
  - MELAS
- Arrhythmias and conduction defects:
  - KSS
  - PEO
  - MELAS
  - MERRF

Heart → Cardiomyopathy, arhythmia, sudden death

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Available online at www.sciencedirect.com
ScienceDirect
Neuromuscular Disorders 23 (2013) 907–910
www.elsevier.com/locate/nmd

Case report

An "inflammatory" mitochondrial myopathy. A case report

Michelangelo Mancuso [a,*], Daniele Orsucci [a], Elena Caldarazzo Ienco [a], Giulia Ricci [a], Greta Ali [b], Adele Servadio [b], Gabriella Fontanini [b], Massimiliano Filosto [c], Valentina Vielmi [c], Anna Rocchi [a], Lucia Petrozzi [a], Annalisa LoGerfo [a], Gabriele Siciliano [a]

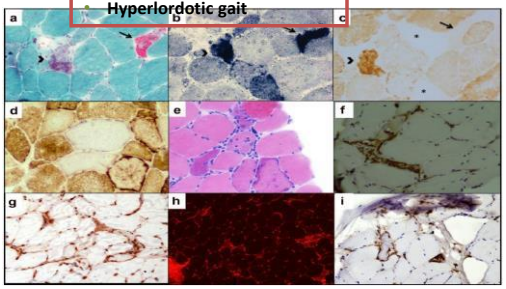
[a] Neurological Clinic, University of Pisa, Italy
[b] Department of Surgery, Division of Pathological Anatomy, University of Pisa, Italy
[c] Neurological Institute, University of Brescia, Italy

Sudden death: case report

♂ 59-year-old

- Ophthalmoplegia
- Ptosis
- Upper limbs muscle weakness
- Hyperlordotic gait

Present since he was 45



Family history of SUDDEN DEATH!

Laboratory exams

Hyperlactacidemia (65,9 mg/dl; normal <25,2); lactate increase after ischemic forearm exercise (124,9 mg/dl; normal <22.2); CK blood elevation (282 U/L; normal <170)

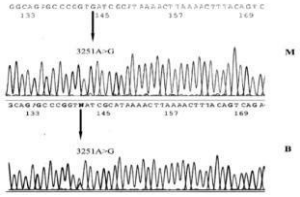
Instrumental exams

Electromyography: myopathic findings
Visual evoked potentials: normal
Pulmonary function: reduced MIP and MEP
ECG and echocardiogram: normal

Muscle biopsy: ragged-red fibers associated to discrete inflammatory infiltrates and necrotizing features

At age 57, he developed a **SUDDEN RESPIRATORY FAILURE**.

- Immediate intubation and artificial ventilator support
- Administration of intravenous **IMMUNOGLOBULIN TREATMENT** at standard dosage
- carnitine



SIGNIFICANT CLINICAL IMPROVEMENT

He was discharged one month after, and tracheostomy tube was removed few months later

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FROM THE HEART……TO THE BRAIN

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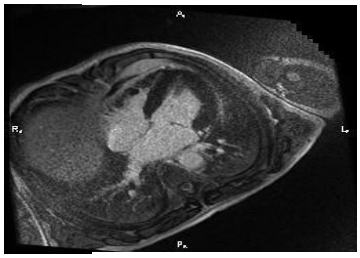
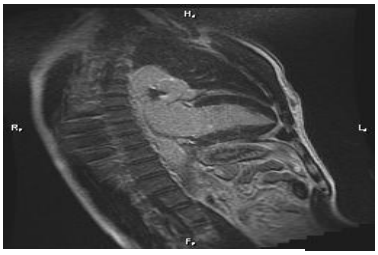
Case 1: ♂ 57 years old

Case 2: ♂ 47 years old

Left ventricular hypertrophy





But also…

angiokeratomas
burning dysesthesia
tinnitus
Renal failure
gastrointestinal disorders

hearing loss
burning dysesthesia
diabetes
diabetic nephropathy
WPW

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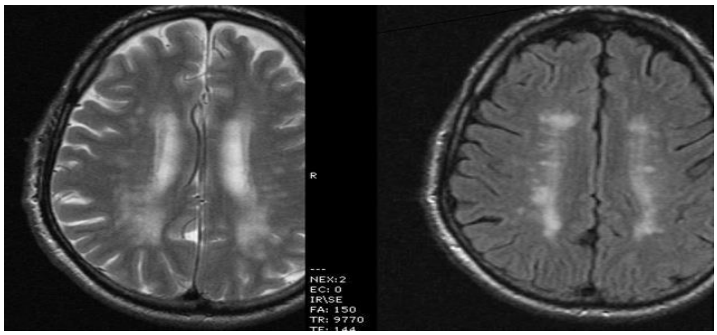
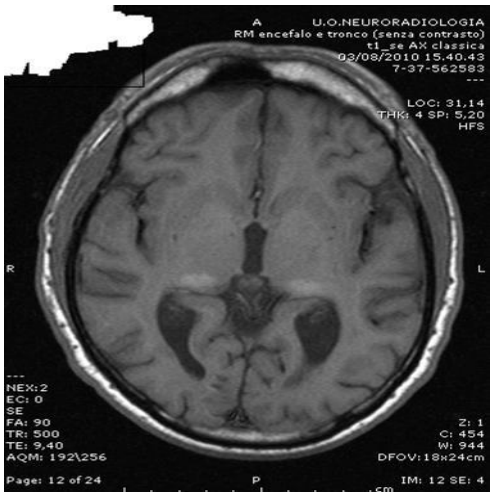
Case 1





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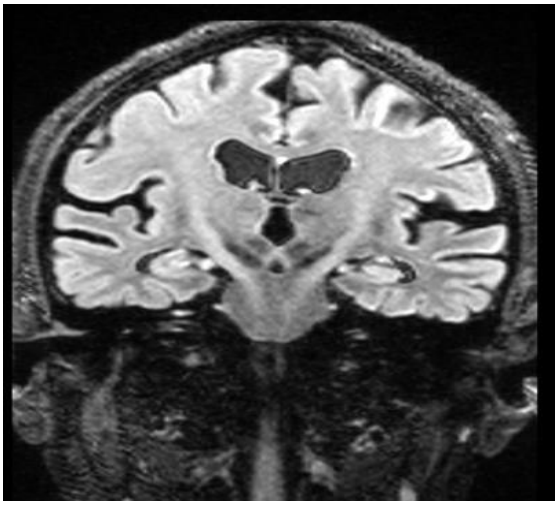
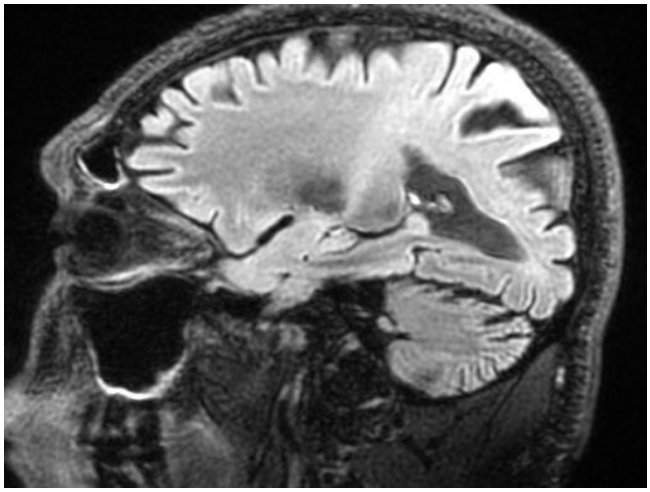
Case 2





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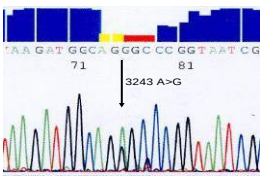
DNA analysis

Case1:

Fabry disease

Case 2:

3243 A>G mt DNA mutation



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Symptom Review: GI & Endocrine

- GI:
  - Anorexia
  - Early Satiety
  - Failure to Thrive
  - Abdominal Pain
  - Gastroesophageal Reflux
  - Bloating
  - Abdominal Distention
  - Pseudo-Obstruction
  - Constipation
  - Cyclic Vomiting
- Liver:
  - Hepatomegaly
  - Dysfunction
  - Fatty Liver
  - Cirrhosis
  - Coagulopathy
- Pancreas:
  - Pancreatic dysfunction
- Endocrine
  - Diabetes
  - Short stature
  - Dysthyroidism
  - Progressive reduction in BMI

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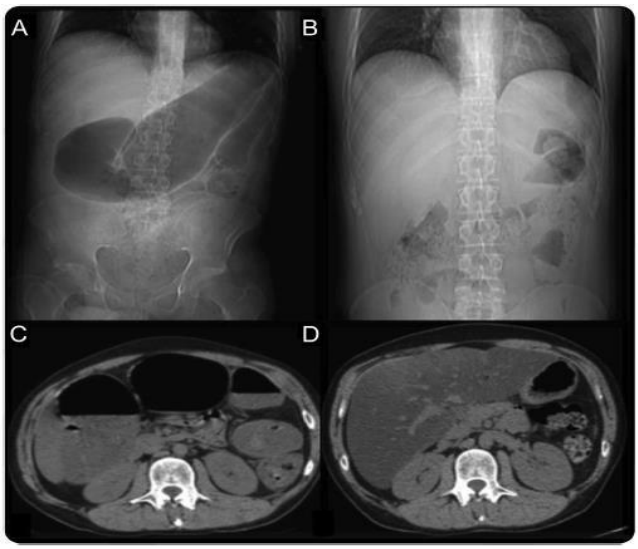
Neurology 82 May 27, 2014

ACUTE REFRACTORY INTESTINAL PSEUDO-OBSTRUCTION IN MELAS: EFFICACY OF PRUCALOPRIDE

In mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), a multisystem mitochondrial disorder, gastrointestinal involvement is frequent with dysphagia, chronic diarrhea, anorexia, abdominal pain, delayed gastric emptying, and paralytic, often intractable, ileus.[1] In this article, we report a patient with chronic gastrointestinal dysmotility and acute refractory intestinal pseudo-obstruction responsive to prucalopride.

Guido Primiano, MD
Domenico Plantone, MD
Fabrizio Forte, MD
Donato Sauchelli, MD
Franco Scaldaferri, MD
Antonio Gasbarrini, MD
Serenella Servidei, MD



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PERGAMON

Neuromuscular Disorders 11 (2001) 7–10

www.elsevier.com/locate/nmd

Review article

MNGIE: from nuclear DNA to mitochondrial DNA

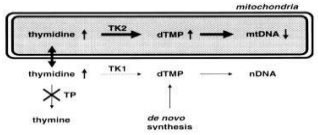
Ichizo Nishino[1,*], Antonella Spinazzola, Michio Hirano

Department of Neurology, Columbia University, New York, NY 10032, USA

Received 19 January 2000; received in revised form 12 May 2000; accepted 16 May 2000

Table 1
Clinical features of MNGIE

Cachexia	100% (35/35)
Gastrointestinal manifestations	100% (35/35)
Borborygmi	96%
Abdominal pain	94%
Diarrhea	93%
Early satiety	93%
Diverticulosis	67%
Pseudo-obstruction	65%
Neurological manifestations	100% (34/34)
Ptosis	100%
Ophthalmoplegia	100%
Peripheral neuropathy	100%
Hearing loss	45%



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Liver:

Mitochondrial liver disease can present **acutely** in a child with no history of hepatic dysfunction, or with **chronic** liver and CNS disease.
Liver disease accompanied by chronic neuromuscular disease or disease in other organ systems may be a sign of mitochondrial disease.

Cronic: manifested by

- Elevated aminotransferases
- Hepatomegaly
- Cholestasis
- Cirrhosis
- Steatosis

These may be accompanied by other indicators of mitochondrial disease including hypoglycemia or lactic acidosis.

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Acute: fulminant or acute liver failure is one important presentation of mitochondrial disease. Especially in a young child or in one with pre-existing or disproportionate central nervous system (CNS) involvement, mitochondrial disease is in the differential diagnosis of acute liver failure.

In children with unknown **status epilepticus** treated with **valproic acid** and developing **acute liver failure**, Alpers syndrome (POLG) should be suspected

AVOID VALPROIC ACID IN POLG

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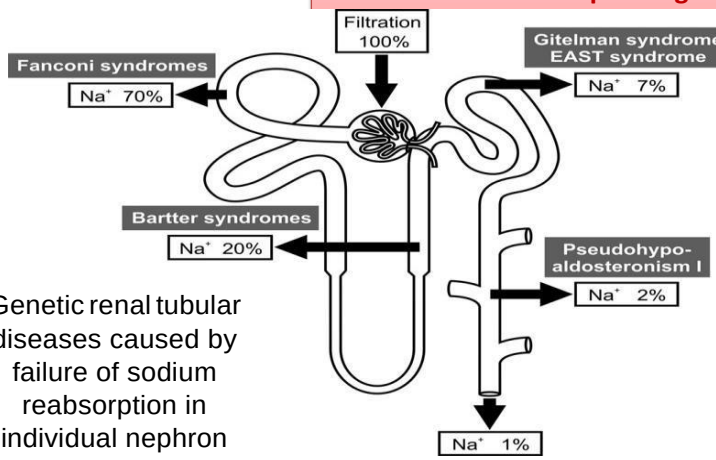
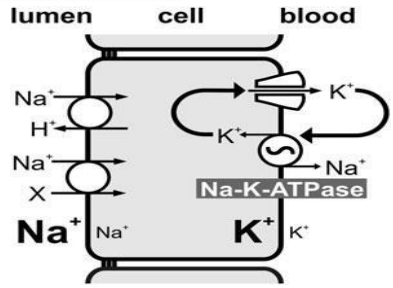
Renal function: renal tubular insufficiency, Fanconi Syndrome, renal cysts

Fanconi Syndrome:

low-molecular weight proteinuria, aminoaciduria, glycosuria and phosphaturia with consequent rickets
but no evidence of impaired glomerular filtration



Genetic renal tubular diseases caused by failure of sodium reabsorption in individual nephron segments.



Simplified schematic of renal proximal tubular cell with key transepithelial transport systems

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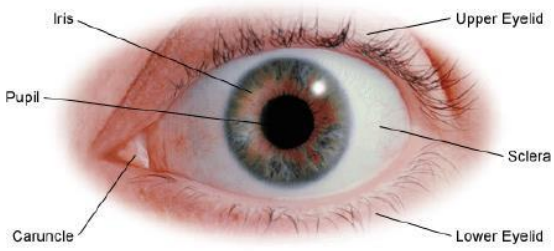
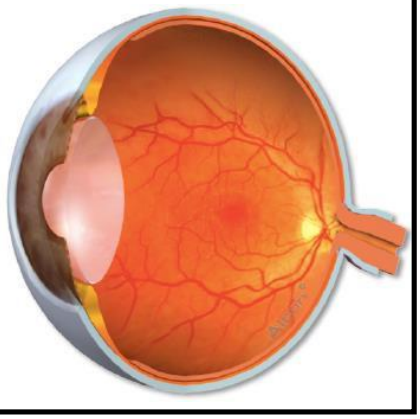


50% of MDs patients



Cataract
Ptosis
PEO
Pigmentary retinopathy
Optic nerve atrophy

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FUNDUS OCULI EXAMINATION: LHON

- preceding or during the acute stage of vision loss, there can be characteristic findings, including optic disc hyperemia, peripapillary telangiectatic blood vessels, vascular tortuosity, and swelling of the retinal nerve fiber layer around the optic disc without corresponding leakage on fluorescein angiography (“pseudoedema”).

FO NORMAL AT THE ONSET UP TO 20%

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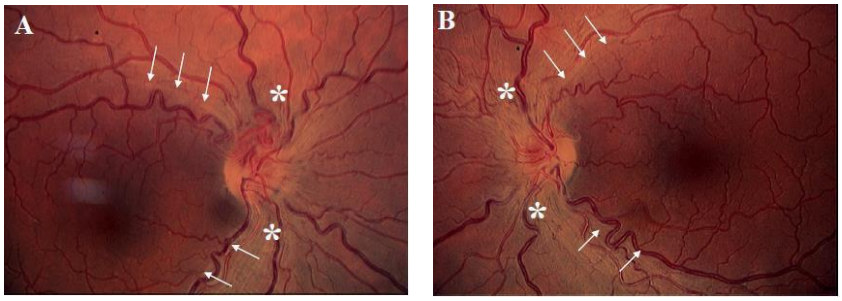
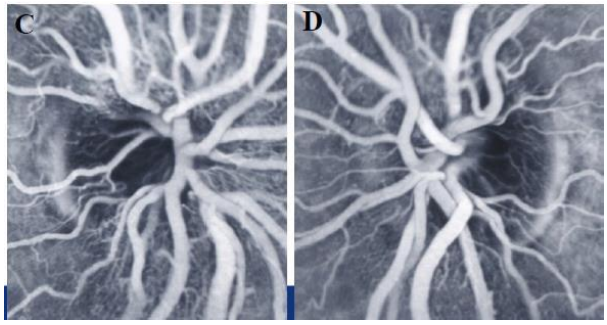
peripapillary telangiectatic blood vessels, vascular tortuosity



swelling of the retinal nerve fiber layer around the optic disc without corresponding leakage on fluorescein angiography (“pseudoedema”)



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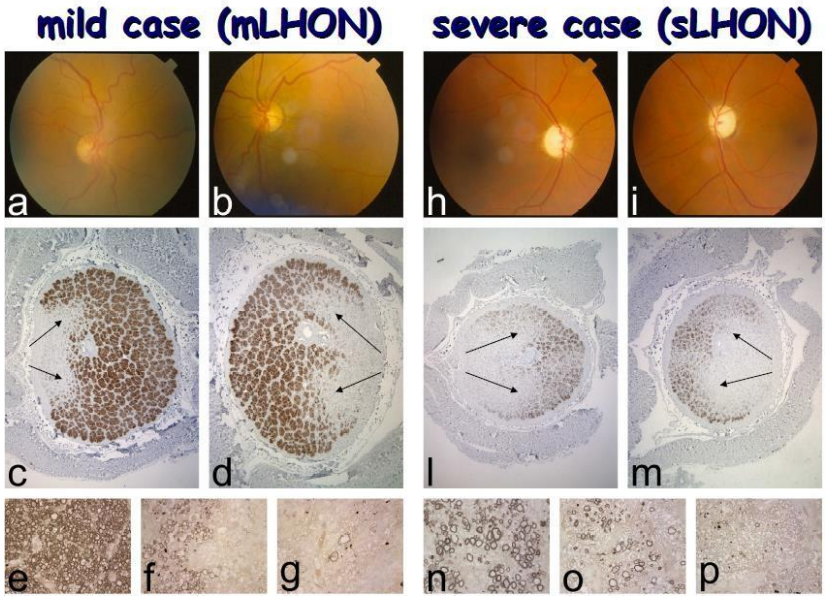

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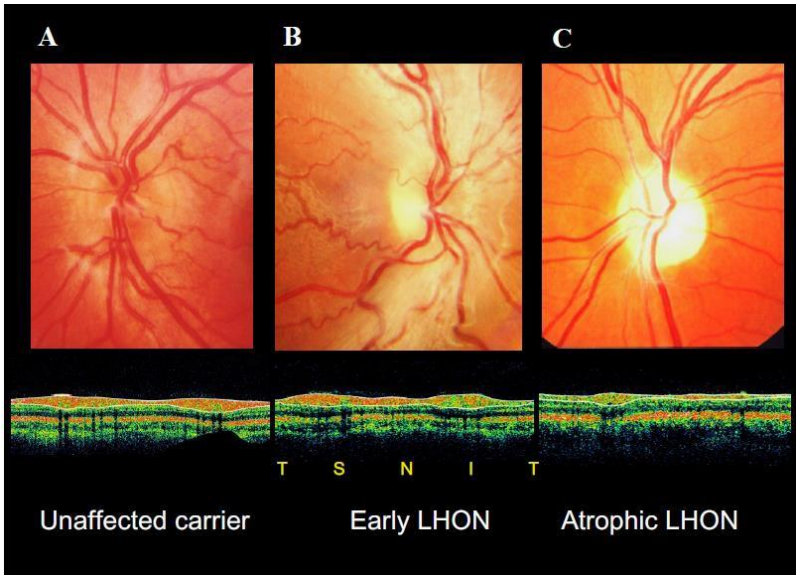

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Symptom Review: skin, blood

- Skin:
  - Pallor, Blotchiness, Mottling without Provocation
  - Erythromyalgia
  - Easy Bruising
  - Multiple lipomatosis
- Blood:
  - Anemia
  - Sideroblastic Anemia
  - Neutropenia
  - Thrombocytopenia

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frontiers in Neurology

ORIGINAL RESEARCH
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Lipomatosis Incidence and Characteristics in an Italian Cohort of Mitochondrial Patients

Olimpia Musumeci[1*†], Emanuele Barca[2†], Costanza Lamperti[3], Serenella Servidei[4], Giacomo Pietro Comi[3], Maurizio Moggio[5], Tiziana Mongini[7], Gabriele Siciliano[8], Massimiliano Filosto[9], Elena Pegoraro[10], Guido Primiano[4], Dario Ronchi[3], Liliana Vercelli[7], Daniele Orsucci[3], Luca Bello[10], Massimo Zeviani[11], Michelangelo Mancuso[3] and Antonio Toscano[1]

1,7%

FIGURE 1 | Schematic representation of lipomas distribution in the study population. In the boxes the frequency of observations in the cohort.

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LABORATORY TESTS

- Labs:
  - Liver Function Tests
  - CPK: normal or moderately elevated in patients with MDs. One notable exception is the myopathic form of the mtDNA depletion syndrome (TK2)
  - Urine Myoglobine: Some mito-patients (i.e. patients with cytochrome b mutations) may occasionally manifest with acute episodes of rhabdomyolysis with myoglobinuria
  - Fasting Serum Glucose
  - Ammonia
  - Amino Acids
  - Serum Thymidine: elevated in MNGIE (specific deficiency of thymidine phosphorylase)
  - Lactic Acid
  - UOA

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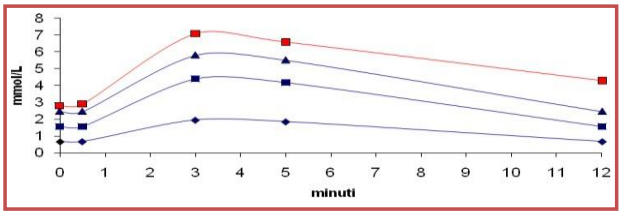
Lactic acid

The key features of a mitochondrial myopathy are a low anaerobic threshold, indicating impaired oxygen utilization, and an increased respiratory exchange ratio because of an inefficient utilization of fatty acids as an energy source

Forearm ischemic test



However, lactic acidosis should not be considered an absolute requisite for diagnosis; there are multiple mitochondrial diseases in which blood lactic acid is often normal or only mildly increased.

Increased lactate may also be detected in the cerebrospinal fluid (CSF).

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Elevated **lactate-to-pyruvate (L:P) ratio** may indicate inherited disorders of the respiratory chain complex, tricarboxylic acid cycle disorders and pyruvate carboxylase deficiency. Respiratory chain defects usually result in L:P ratios >20.

A low L:P ratio may indicate an inherited disorder of pyruvate metabolism. Defects of the pyruvate dehydrogenase complex result in L:P ratios <10

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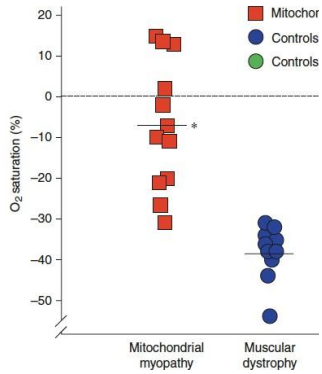
Fig. 3 Exercise induced change in venous oxygen saturation. Individual peak changes in cubital venous oxygen saturation during handgrip exercise in 12 patients with mutation of mtDNA, 10 patients with muscular dystrophy, and 12 age- and gender-matched healthy subjects. *, different from both control groups ($p < 0.05$)



Oxigen extraction and $VO2_{max}$ is impaired in MDs

Exercise induced change in venous oxygen saturation

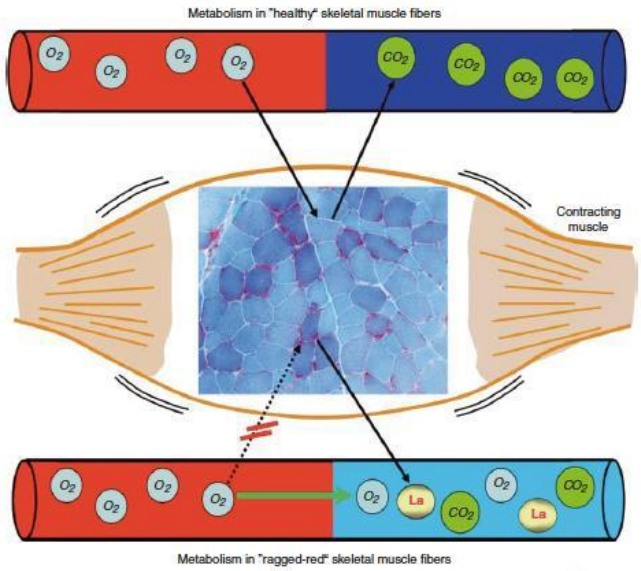


Fig. 8 Differential lactate metabolism in muscle fibers with low and high mutation loads. The figure illustrates how lactate in one muscle fiber can be efficiently oxidized (in muscle fiber with low mtDNA mutations and thus intact oxidative capacity), while lactate is released from fibers with high mtDNA mutation load, explaining a simultaneous high lactate release in muscle fibers with high mtDNA mutation burden vs. high lactate oxidation capacity in fibers with low mutation loads

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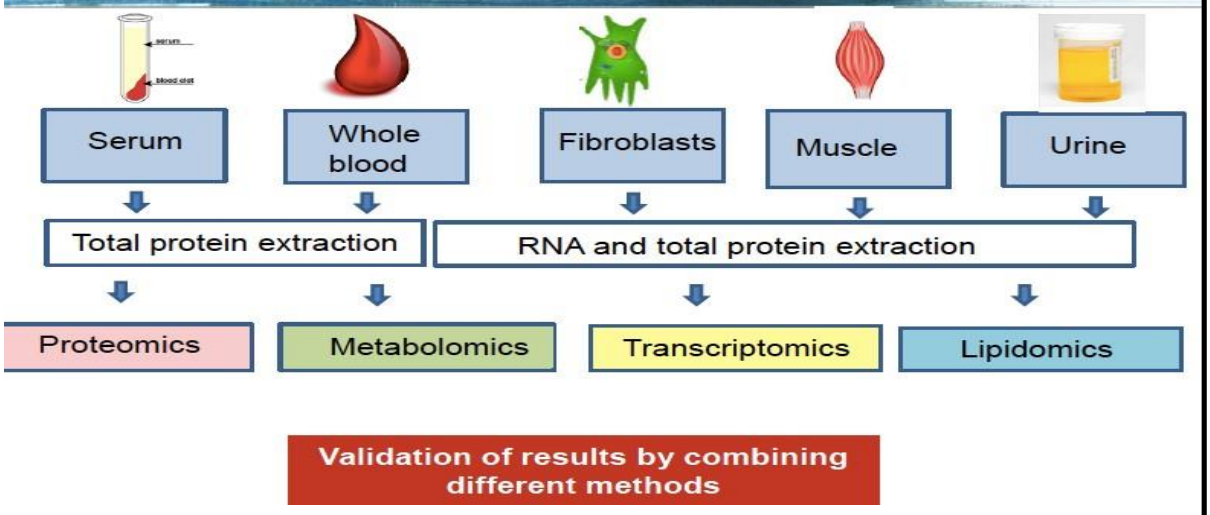
Biomarkers: diagnostic, pharmacokinetic, prognostic, therapy monitoring



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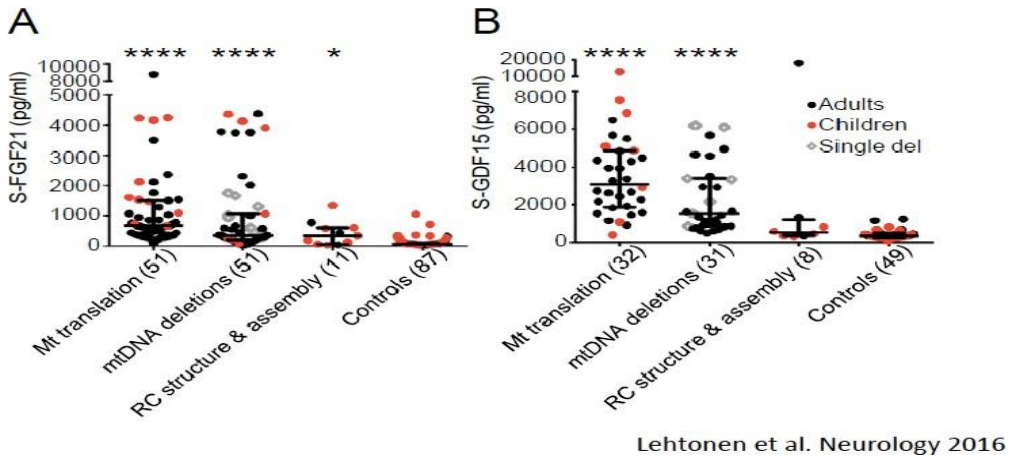
FGF21 and GDF15 are biomarkers of abnormal mitochondrial translation and mtDNA deletions



Lehtonen et al. Neurology 2016

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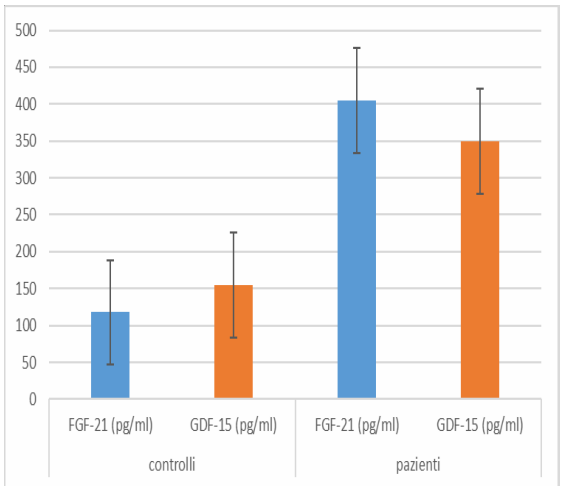
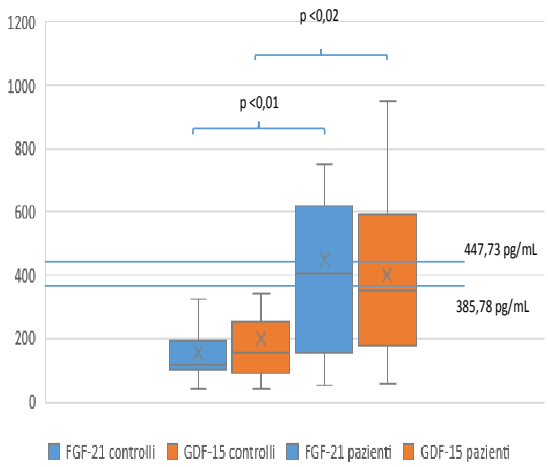
VALUES IN PISA





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Neuroradiological features

To date, no pathognomonic correlation between specific genetic defect and neuroimaging findings have been described…

…but…

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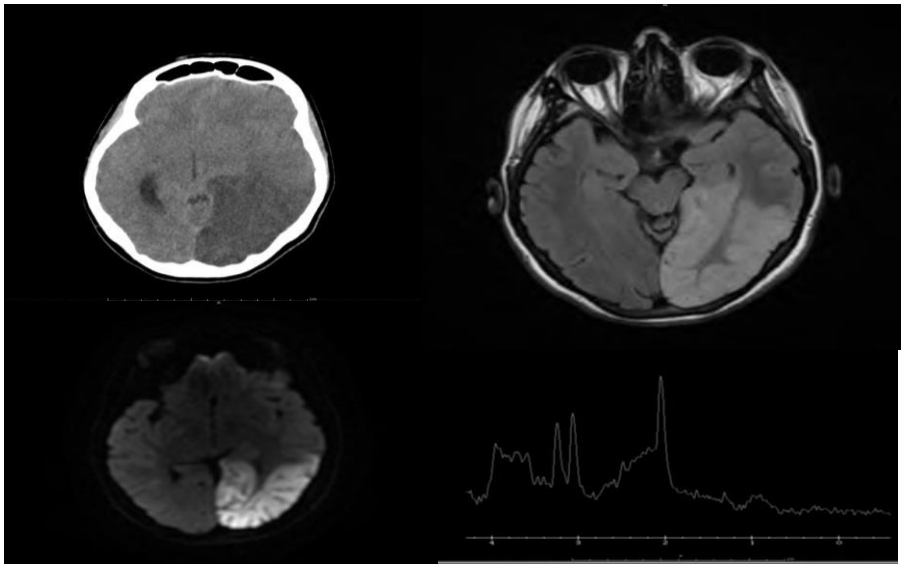
MELAS: stroke-like episodes → **Tipical case**

Age 19:
Migraine, aphasia, hemianopia



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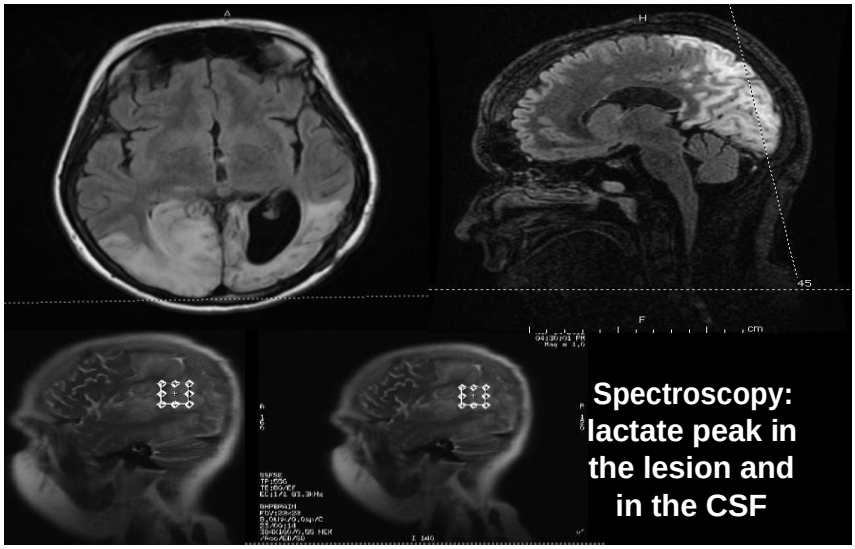
Age 20: Migraine, cortical blindness and status epilepticus partial



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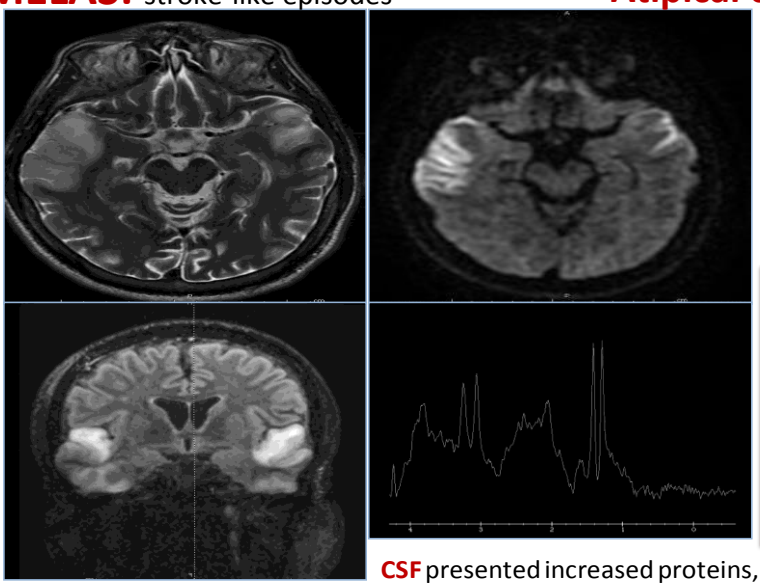
MELAS: stroke-like episodes → **Atipical case**



♂ 45 years

ER: episodes of **confusion** and **headache** in last 3 weeks, two **generalised seizures** followed by **coma** (GCS 5).

family history: negative for neuromuscular or neurodegenerative disorders

Medical history: **hearing loss**

Brain MRI temporal lobes T2 hyperintensity with diffusion restriction and contrast uptake and bilateral globus pallidus and caudate nucleus T1 hyperintensity. Proton spectroscopy showed a lactate peak with reduction of N-Acetyl-Aspartate.

CSF presented increased proteins, glucose and **lactate** but not white cells. Increased **lactate** was also present in serum

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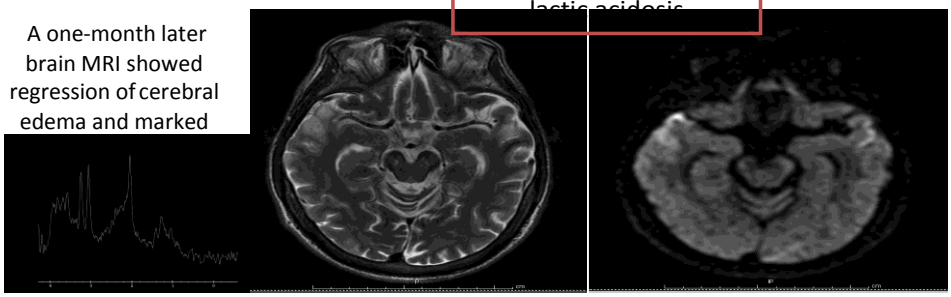
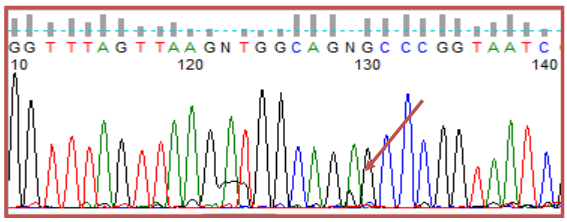
LEV, **carnitine** and 600 mgs of **coenzyme Q10**

Rapid clinical improvement (GCS 13) and regression of the lactic acidosis

A one-month later brain MRI showed regression of cerebral edema and marked



Genetic testing showed the 3243A> G mtDNA mutation in urine, compatible with MELAS syndrome



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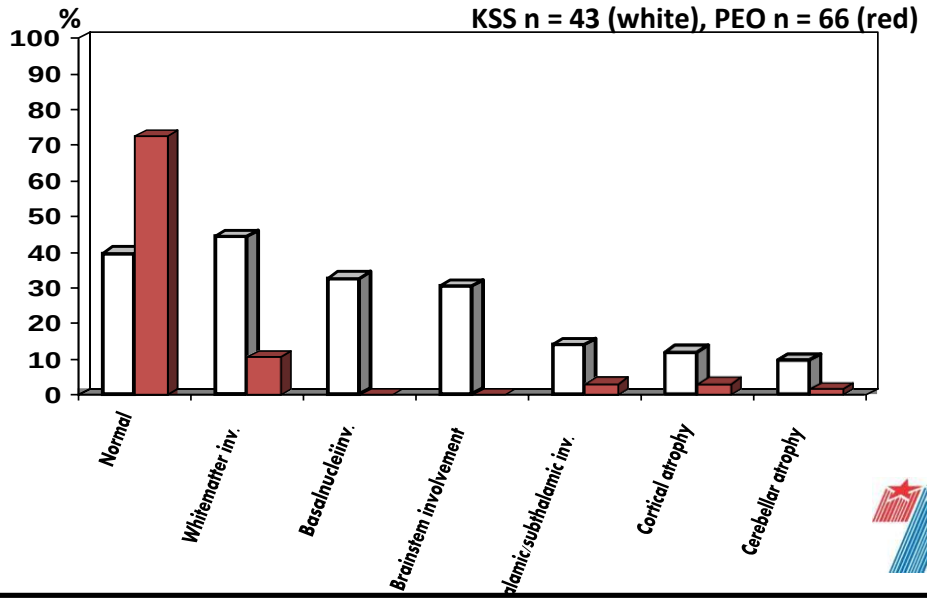
RESULTS: mtDNA single deletion neuroradiological features



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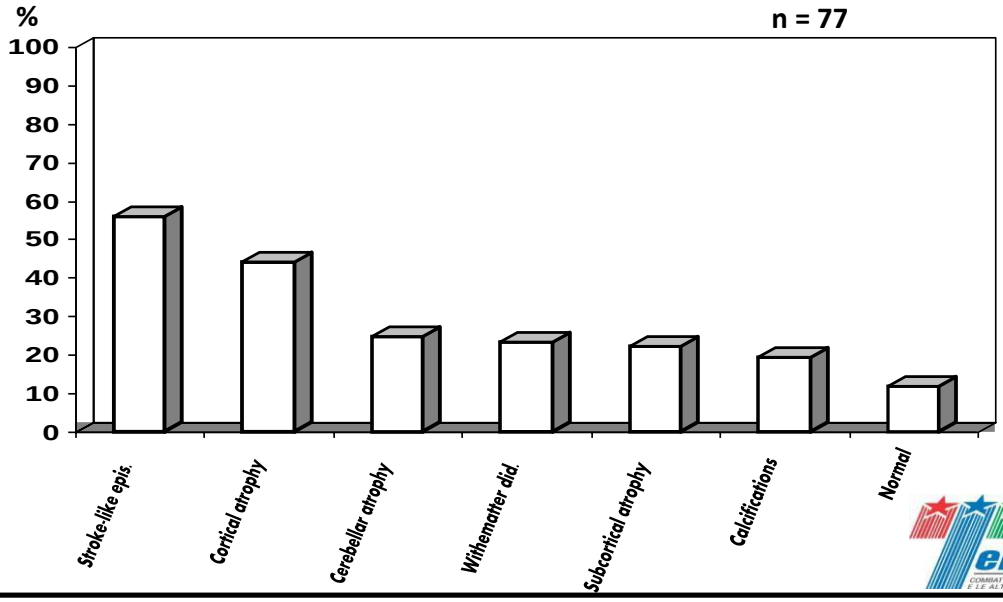
RESULTS: Neuroradiological features m.3243A>G



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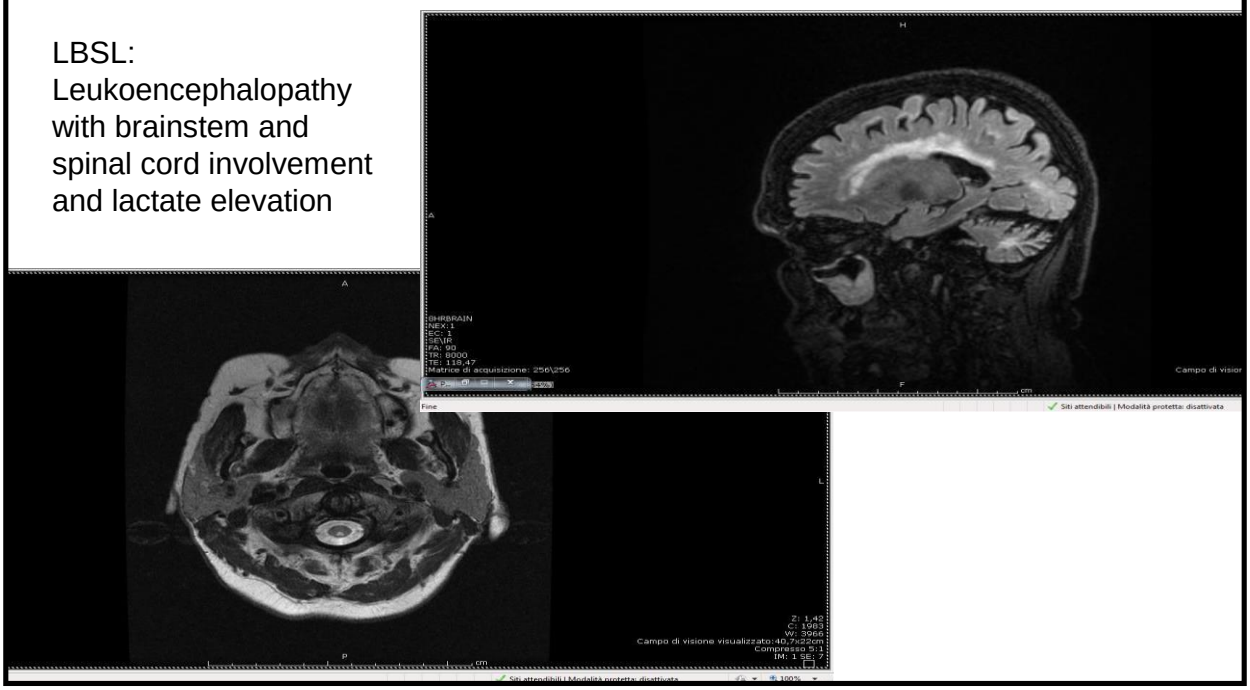
LBSL: Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation



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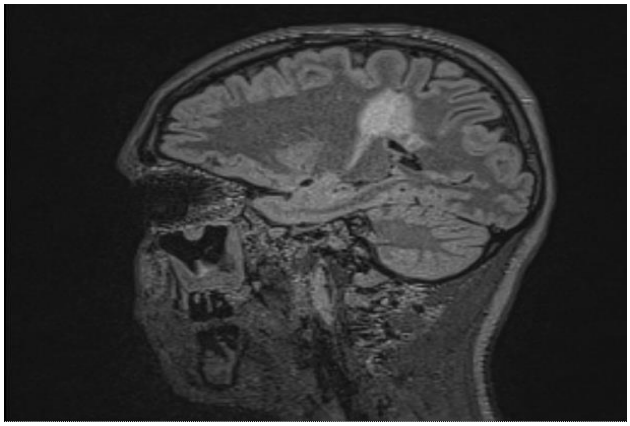
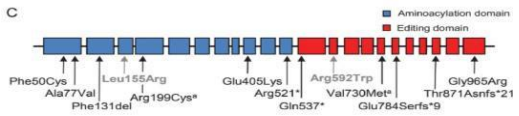
AARS2 mutation: leukodystrophy





AARS2 mitochondrial alanyltRNA synthetase 2 gene

AARS2 mutations recentrly described with infantile hypertrophic cardiomyopathy, lactic acidosis, and brain and skeletal muscle involvement, with early fatal outcome.

Pisa: woman 25 years-old

But not only…

Novel (ovario) leukodystrophy related to *AARS2* mutations

Neurology® 2014;82:2063–2071

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Sietske H. Kevelam, MD*
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Gajja S. Salomons, PhD
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Costanza Lamperti, MD, PhD
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Adeline Vanderver, MD‡
Daniele Ghezzi, PhD‡
Marjo S. van der Knaap, MD‡

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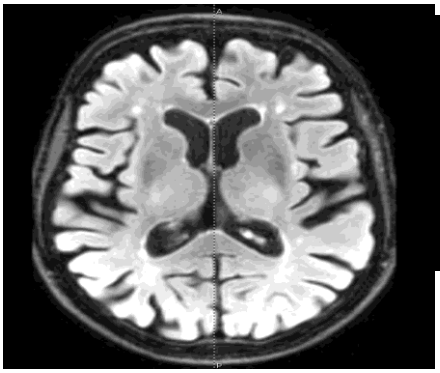
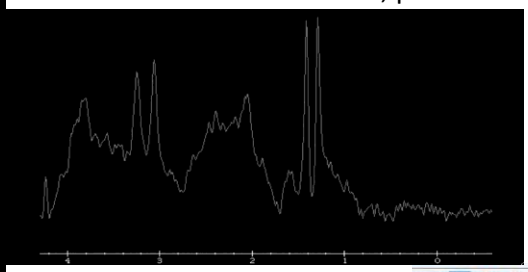
ANT1 mutation

Woman 75 years-old
- Bilateral ptosis
- Ophtalmoparesis
- Shoulders hypostenia
- **Mild cognitive impairment**

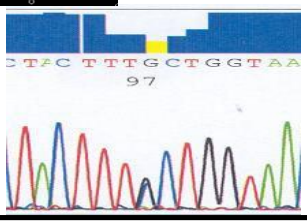
Medical hystory:
- left ventricle hypertrophy
- thyreopathy

Family history: cardiopathy, sudden death, ptosis





c.340G>C exon 2



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When hypothesize a mitochondrial disorder?

Mitochondrial disorders in neurology are either underdiagnosed : “what is this bizarre syndrome?” or overdiagnosed: “this syndrome is so bizarre that it must be mitochondrial”

but

It is a mistake to confound strangeness with mystery. The most commonplace crime is often the most mysterious because it presents no new or special features from which deductions may be drawn. **The strange details, far from making the case more difficult, have really had the effect of making it less so**.”

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Details
Mild signs-symptoms
Multidisciplinary approach
Observe (ie lipomas)!
Associations (i.e.)
-NSHL&DM
-myoclonus&ataxia
-PEO&Parkinsonism
-liver f. &encephalopathy

Deep inside
Lab tests (lactate,aa..)
Radiology

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BEYOND NEUROLOGY
-cardio(myo)pathy
-liver imp.
-diabetes
-NSHL
-lactic acidosis

SNC
-seizures & myoclonus
-ataxia
-cognitive imp.
-stroke like episodes
-movement disorders
-optic atrophy
-NSHL
-psychomotor impairment\hallucinations

NEUROMUSCULAR
-PEO
-Exercise intolerance
-Weakness, fatigue, pain
-wasting
-dysphagia
-numbness\paresthesia

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