Chianciano Terme -13-15 maggio 2022

Malattie mitocondriali : Classificazione e elementi di clinica

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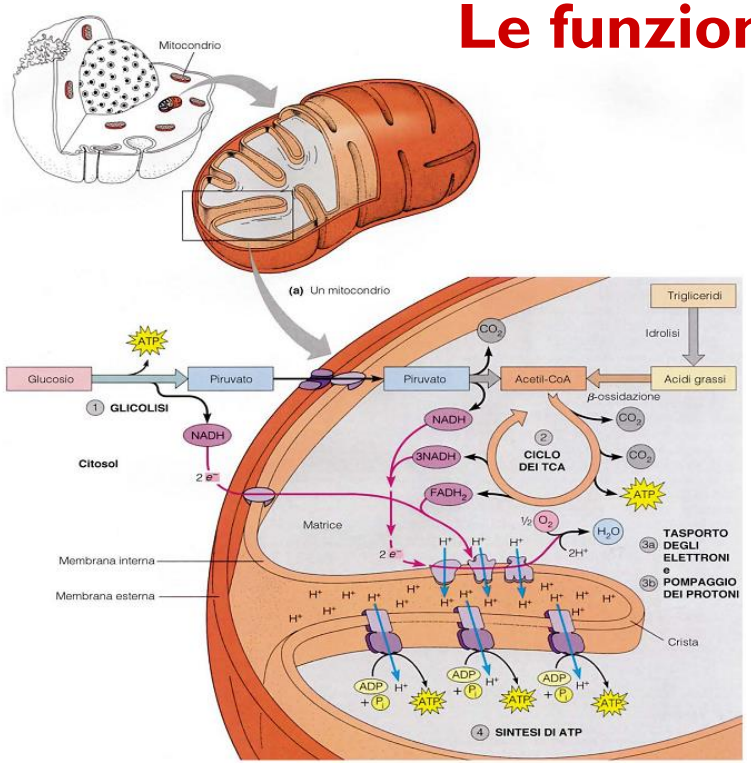
Regione Lombardia

Le funzioni dei mitocondri

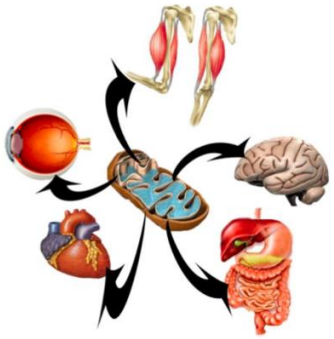


Forniscono energia alla cellula, tramite la fosforilazione ossidativa.

Ospitano importanti pathway metabolici (ciclo di Krebs, β-ossidazione, sintesi dei lipidi e del colesterolo).
Regolano l'omeostasi del Ca^{++}.
Inviano segnali apoptotici.
Ruolo nei processi autofagici

→ ↑ Acido lattico, Radicali liberi
→ ↓ O_2, ATP
→ MORTE CELLULARE

Nelle malattie mitocondriali la corretta funzionalità della catena respiratoria (RC) e del sistema della fosforilazione ossidativa (OXPHOS) è compromessa.



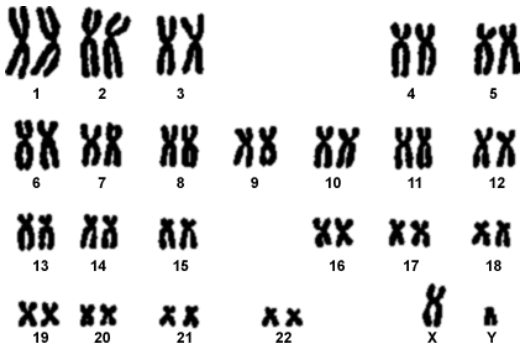
Coinvolge piu' organi: SNC, SNP, fegato, rene, sistema gastrointestinale, sistema ematopoietico sistema endocrino, cardiaco , sistema visivo.

- Presentazione clinica e' variabile con una insorgenza che va dai primi mesi di vita sino ad un esordio in eta' adulta o anche nell'anziano

Le malattie mitocondriali sono considerate il disordine metabolico più frequente.

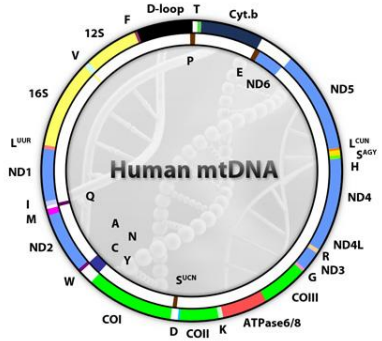
Prevalenza stimata ca. 1:5000-8500 nati.

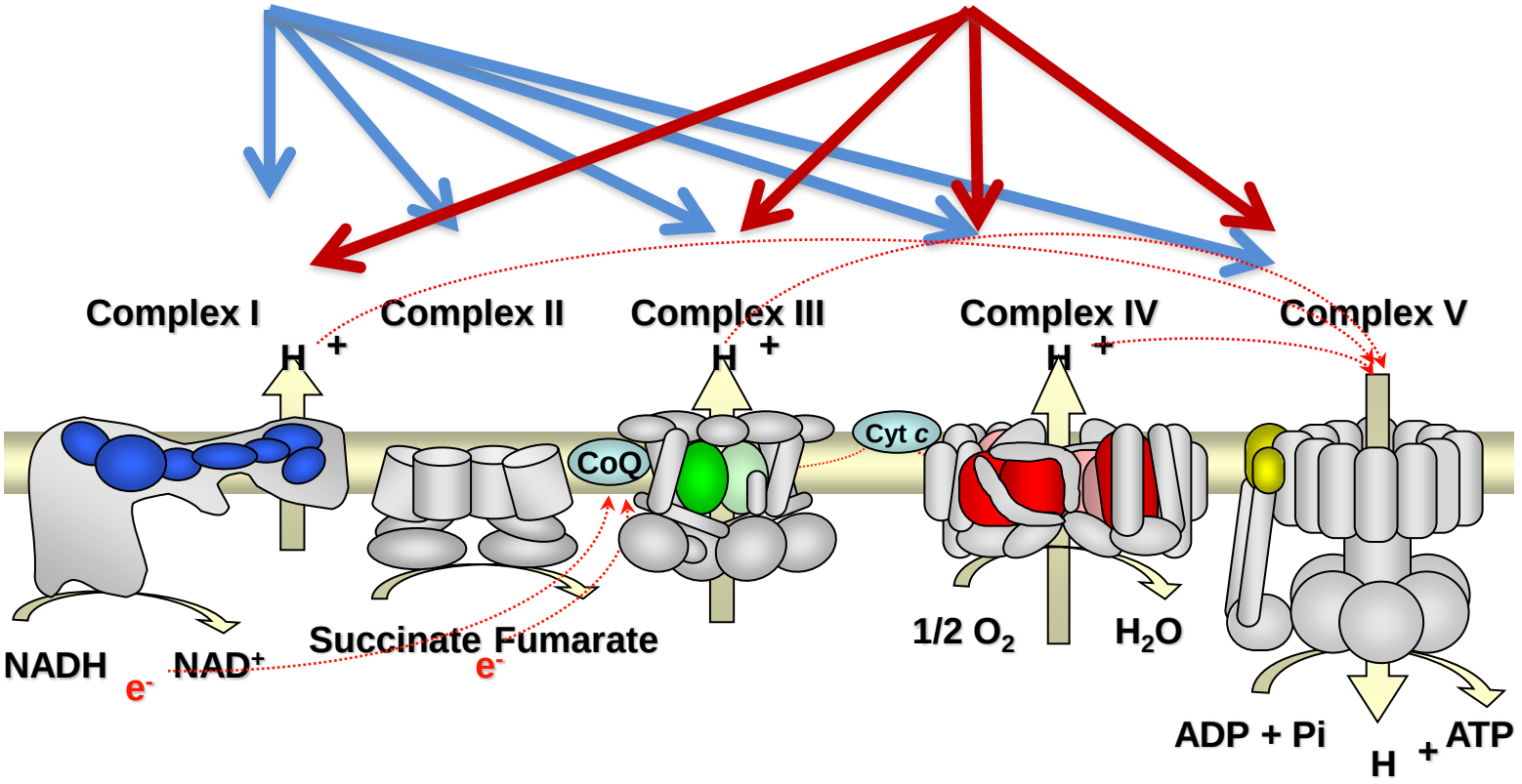
DNA mitocondriale



Replicazione

Riparazione

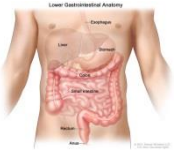




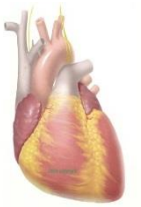
Quando Sospettare una Malattia Mitocondriale

Segni cerebellari
Segni piramidali
Epilessia
Coma
Mioclonie
Episodi stroke-like

Miopatia intolleranza all'esercizio
Mialgia/ crampi
Ipostenia



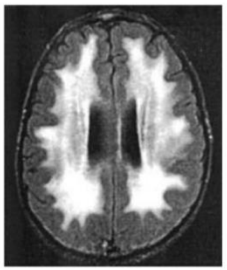
Subocclusioni
Malassorbimento
cachessia



Disturbi de ritmo
Cardiomiopatia

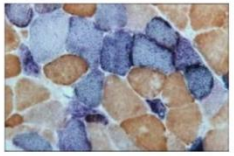
PHENOTYPE

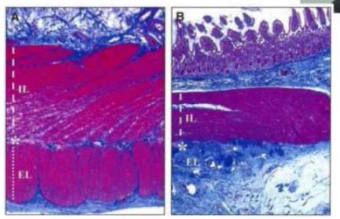
Myo-Neuro-Gastro-Intestinal Encephalomyopathy

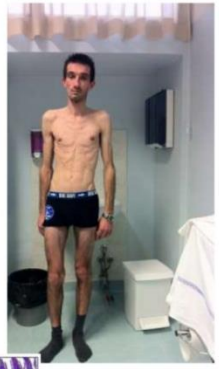


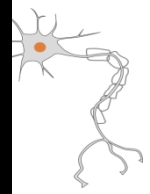
PEO
Neuropathy
Myopathy
Leucoencephalopathy
Cachexia
Infections

MNGIE

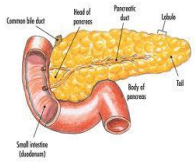






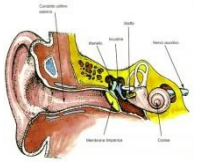


Neuropatie



Diabete
Amenorrea
Bassa statura
Ipertricosi

Neuropatia ottica
PEO
Retinite pigmentosa



Sordità neurosensoriale

Primary Mitochondrial Myopathy PMM

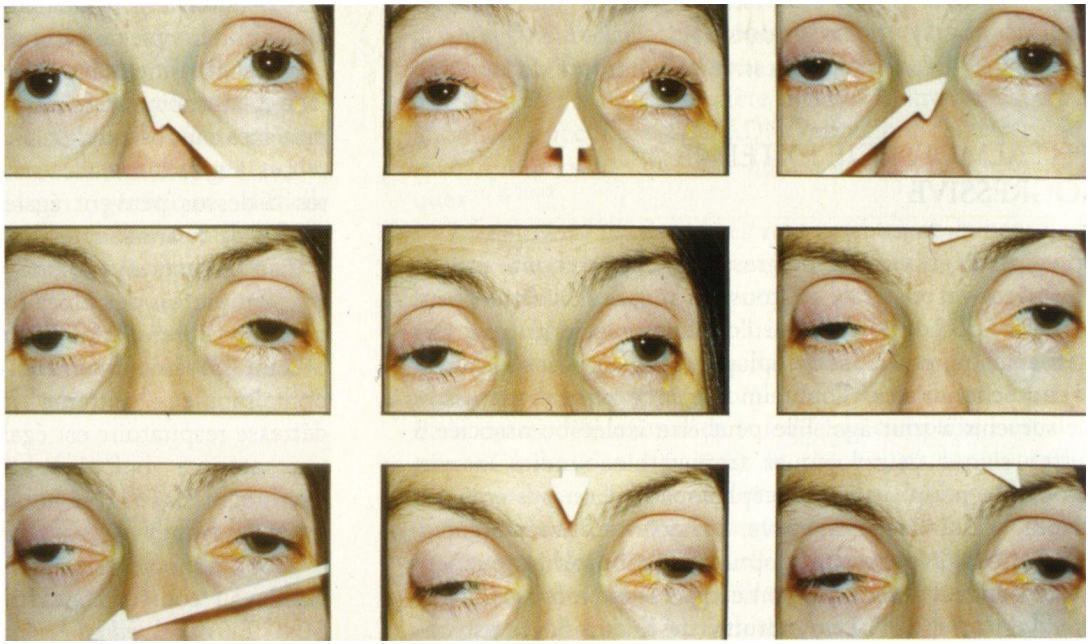
Genetically defined disorders leading to defects of oxidative phosphorylation affecting predominantly, but not exclusively, skeletal muscle (see below for methodology). Secondary involvement of mitochondria, frequently observed in multiple neuromuscular diseases (i.e. inclusion body myositis, Duchenne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

Miopatie

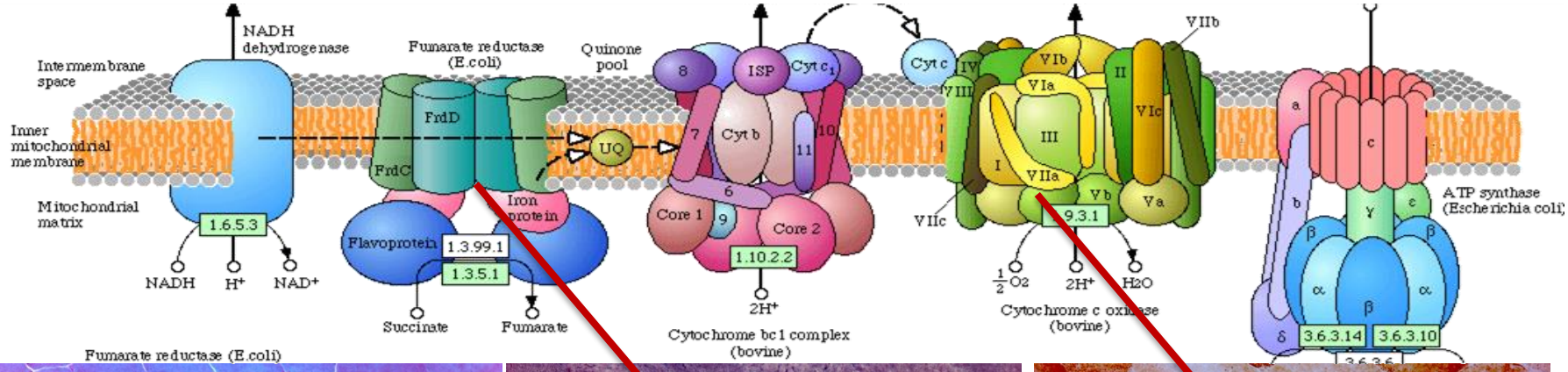
- Crampi mialgie dolori muscolari
- Intolleranza all'esercizio
- Debolezza muscolare
- Disfagia
- Dispnea insufficienza respiratoria

PEO

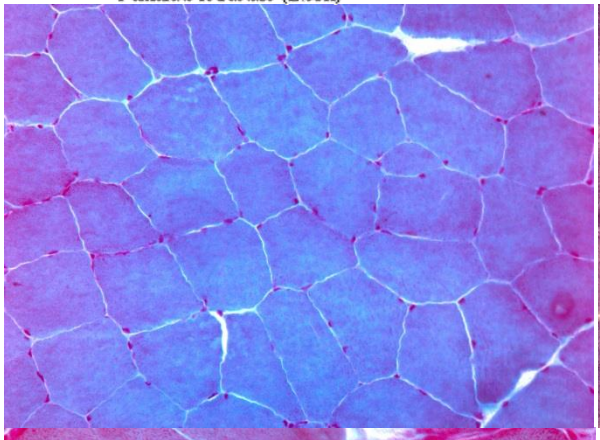
- **Esordio :** seconda –quinta decade
- **Sindrome clinica**: ptosi con oftalmoparesisi +/-miopatia; +/- interessamento SNC, rara diplopia
- **Esami di lab**: CPK elevate, acido lattico elevato ma anche normale.
- **Biopsia muscolare:** Ragged red fibers (RRF): RRF:COX-/SDH+.

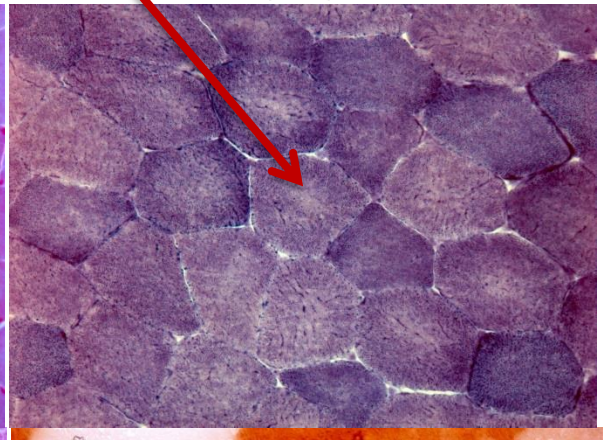


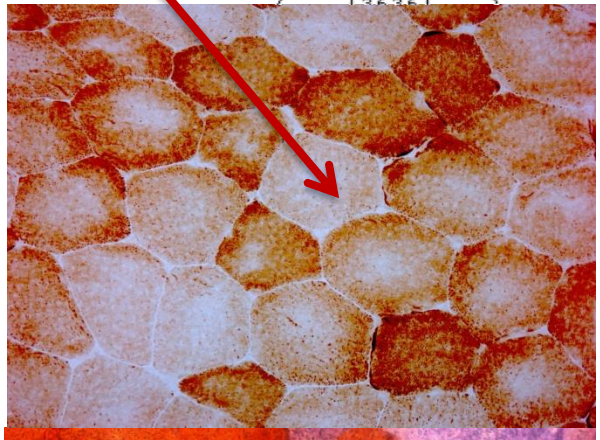
Biopsia Muscolare

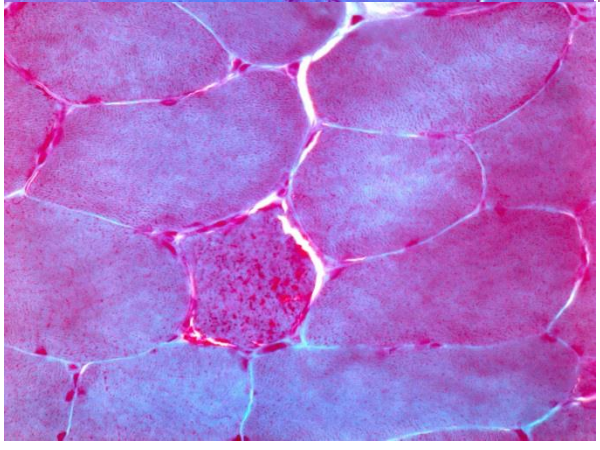


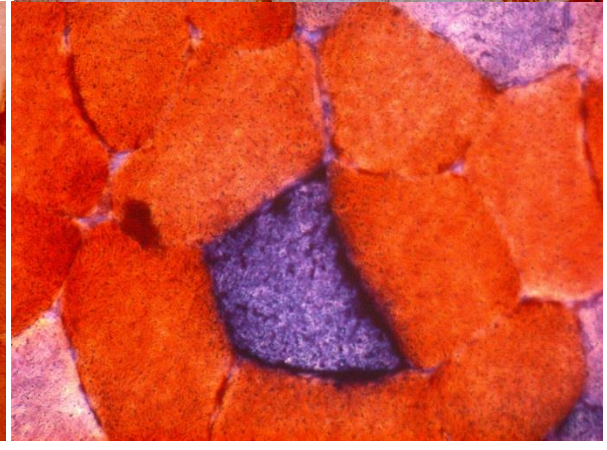
Fumarate reductase (E.coli)

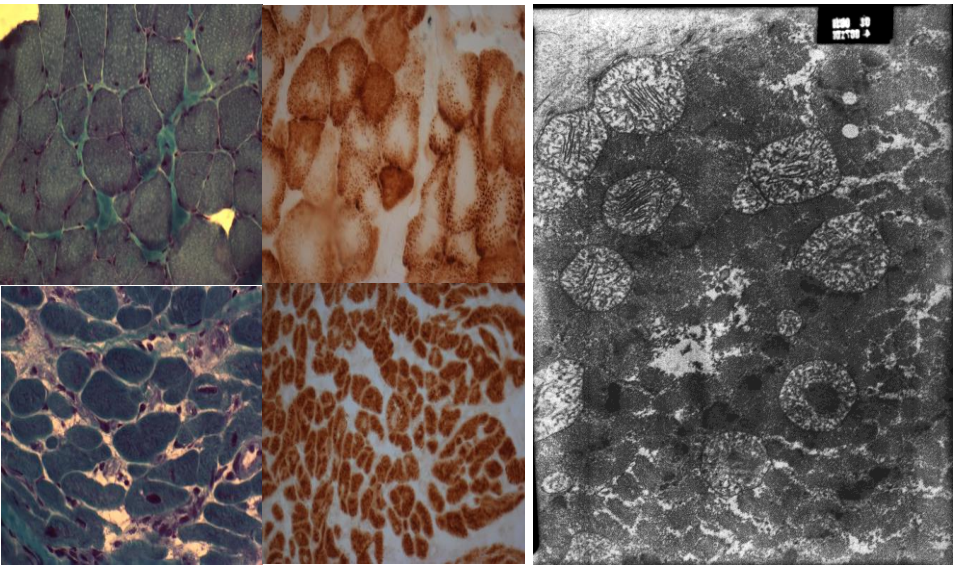




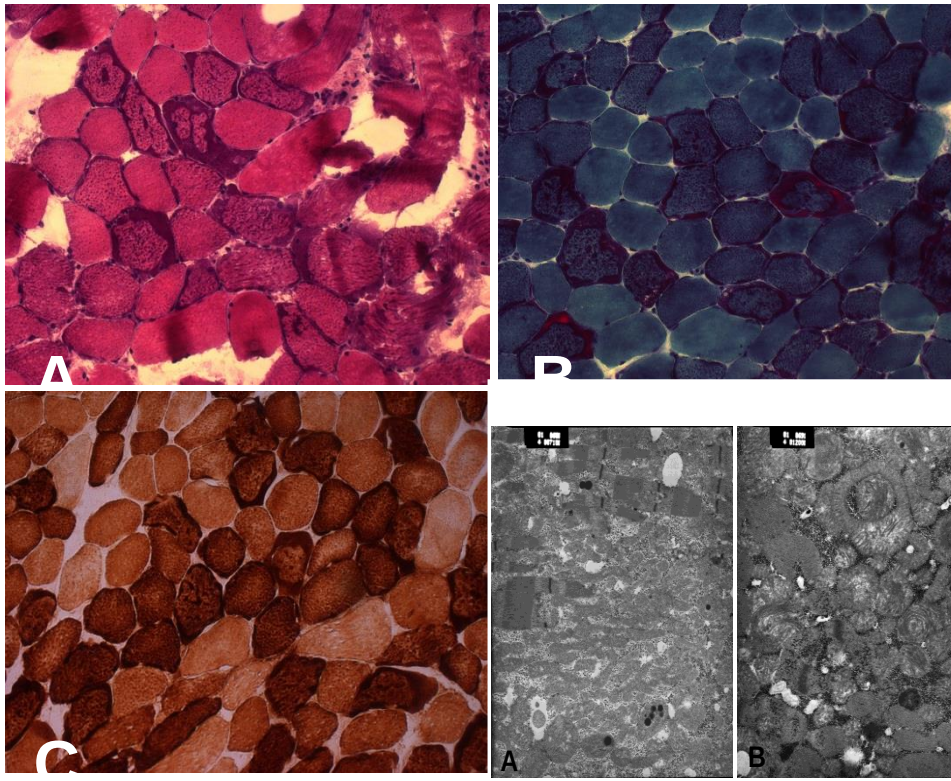




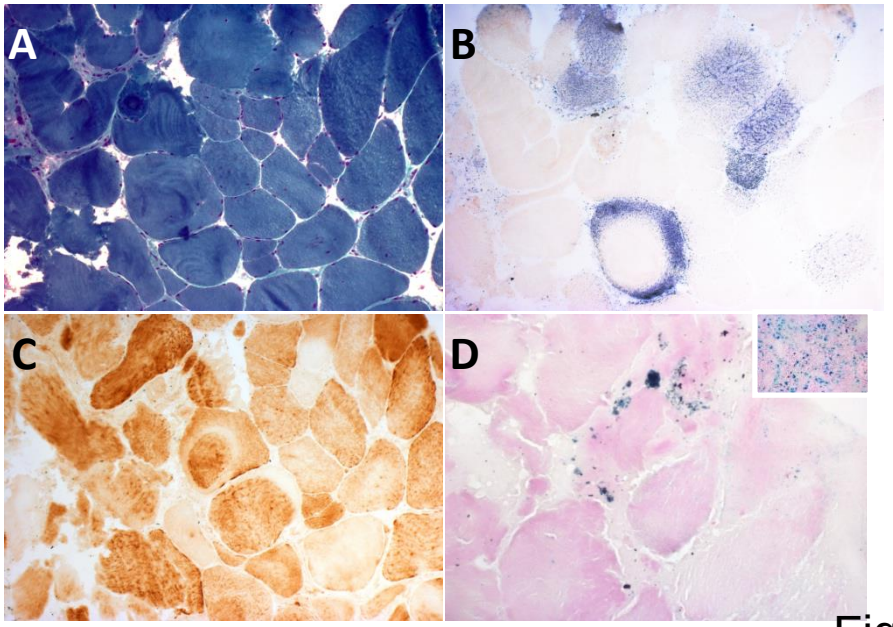




CHKB



mtND2



ISCU

Fig. 1

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ORIGINAL COMMUNICATION

Revisiting mitochondrial ocular myopathies: a study from the Italian Network

D. Orsucci[1,2] · C. Angelini[3] · E. Bertini[4] · V. Carelli[5,6] · G. P. Comi[7] · A. Federico[8] · C. Minetti[9] · M. Moggio[10] · T. Mongini[11] · F. M. Santorelli[12] · S. Servidei[13] · P. Tonin[14] · A. Ardissone[15] · L. Bello[19] · C. Bruno[9] · E. Caldarazzo Ienco[1] · D. Diodato[4] · M. Filosto[16] · C. Lamperti[17] · I. Moroni[15] · O. Musumeci[18] · E. Pegoraro[19] · G. Primiano[13] · D. Ronchi[7] · A. Rubegni[12] · S. Salvatore[8] · M. Sciacco[10] · M. L. Valentino[5,6] · L. Vercelli[11] · A. Toscano[18] · M. Zeviani[17,20] · G. Siciliano[1] · M. Mancuso[1]

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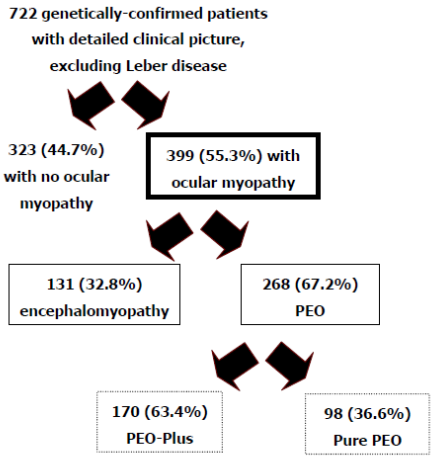
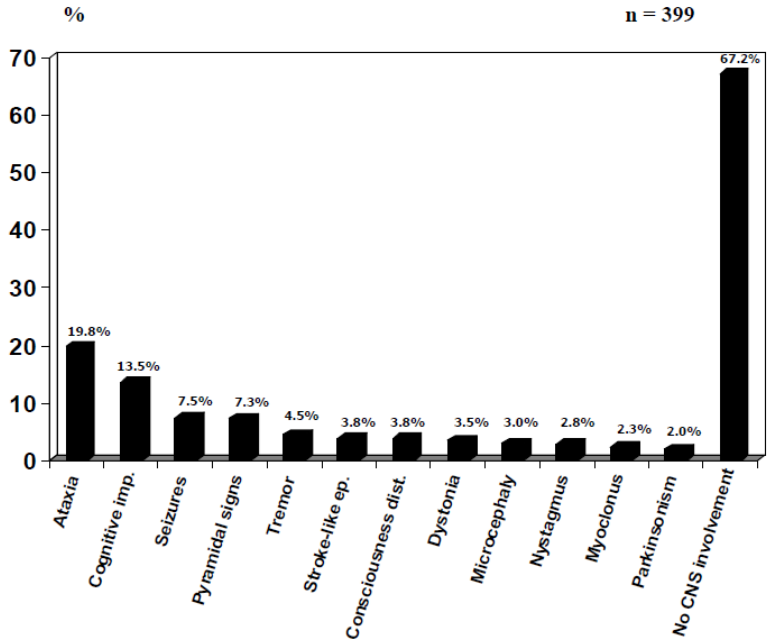




CSN involvement

Symptoms

- Stroke like episodes
- Seazures
- Cognitive involvement
- Ataxia
- Pyramidal signs
- Migrain
- Parkinsinsonis
- Dystonia

Signs

- Stroke like leasons
- Basal ganglial leasons
- Leucodystrophies
- Cerebellar atrophy

Epilepsy

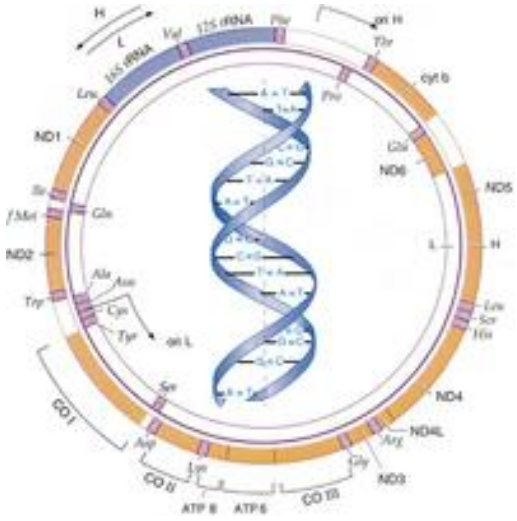
Myoclonus

Ophtalmic seazures

Focal motor seizures

Generalized seizure

Satuts epilepticus



Therapy

Options for mitochondrial epilepsy seem to be a sodium channel blocker (for example, lamotrigine) together with a benzodiazepine (for example, clobazam) and levetiracetam or topiramate as needed.

Usually a multitherapy is needed ,some patients received as many as ten drugs

Mitochondrial patients have a crazy heart

VPA is absolutely contraindicated in patients with mitochondrial epilepsy

MERRF

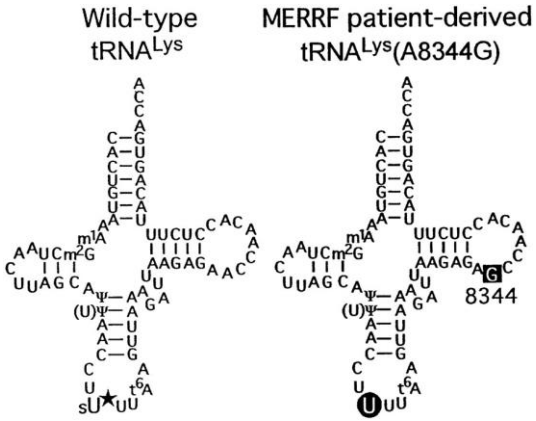
Clinical:

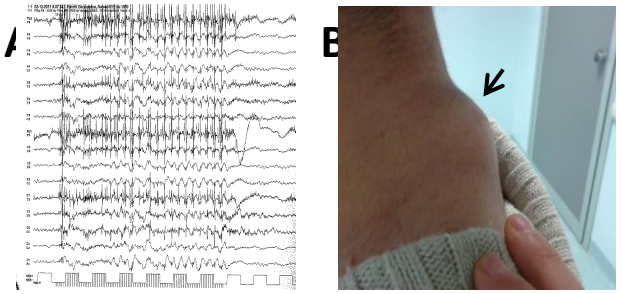
- Onset in childhood/adulthood
- Myoclonic epilepsy
- Muscle weakness
- Hearing loss
- Mental decay
- Multiple Lipomas
- Ataxia

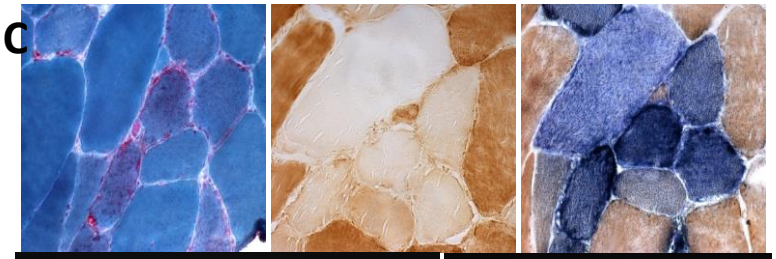
Laboratory: Lactic acidosis, complex IV deficiency

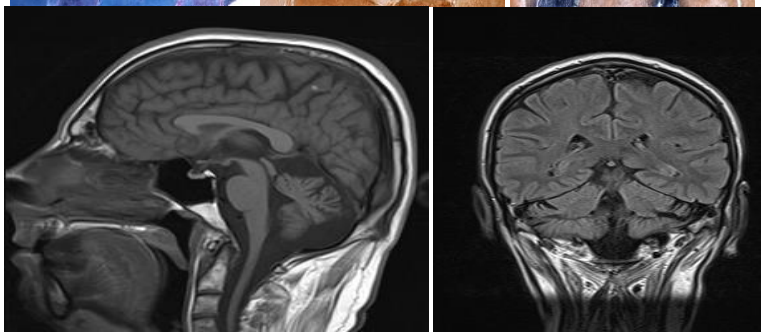
Morphology: RRF

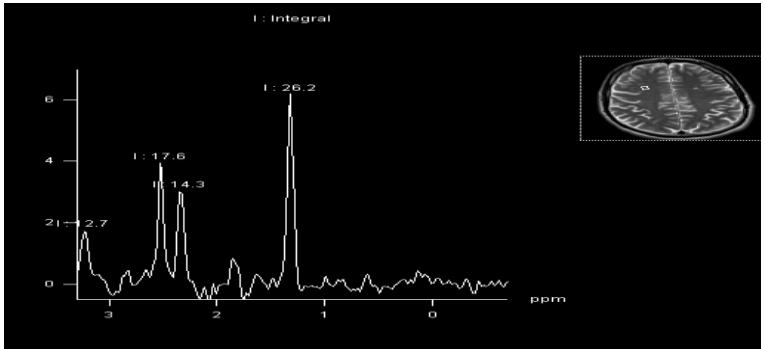
Genetics: Most common mutation A8344G in $tRNA^{Lys}$





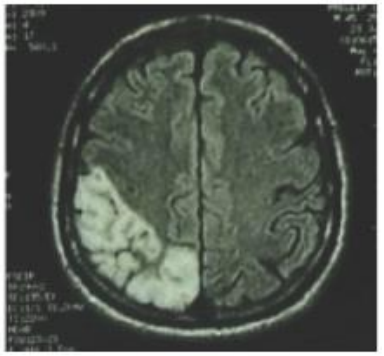






Zeviani M, Lamperti C 2016

MELAS



Migraine, stroke-like, lactic acidosis, demenza, ataxia, epilepsy, myopathy, diabetis, deafness,.

Clinical:

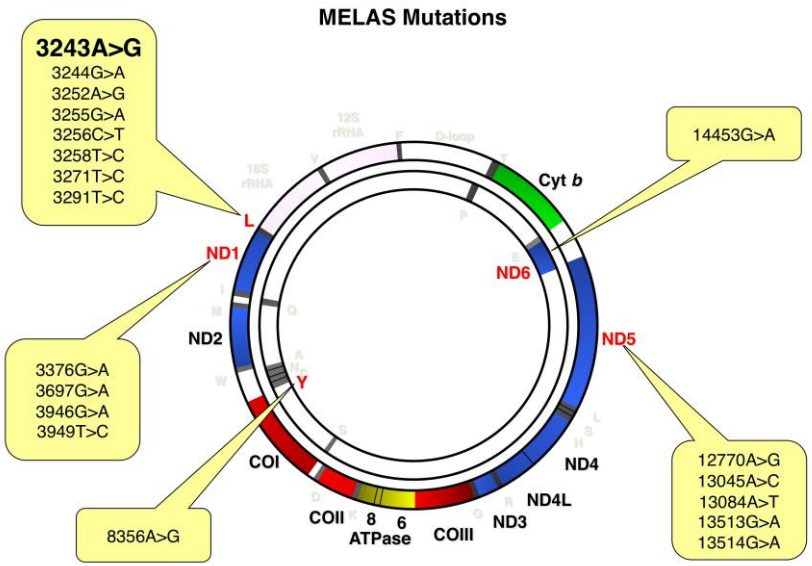
- Onset in childhood/early adulthood
- Stroke-like episodes
- Cortical blindness
- Hearing loss
- Diabetes
- Migraine
- Epilepsy

Laboratory: Lactic acidosis, complex I deficiency

Morphology: RRF

Strongly SDH- +in muscle and blood vessels

Genetics: Most common mutation 3243A>G in $tRNA^{Leu(UUR)}$



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https://doi.org/10.1007/s00415-021-10697-1

ORIGINAL COMMUNICATION

Adult-onset mitochondrial movement disorders: a national picture from the Italian Network

V. Montano[1] · D. Orsucci[2] · V. Carelli[3,4,5] · C. La Morgia[3,4] · M. L. Valentino[3,4,5] · C. Lamperti[6] · S. Marchet[6] · O. Musumeci[7] · A. Toscano[7] · G. Primiano[8,9] · F. M. Santorelli[10] · C. Ticci[10] · M. Filosto[11] · A. Rubegni[10] · T. Mongini[12] · P. Tonin[13] · S. Servidei[8,9] · R. Ceravolo[1] · G. Siciliano[1] · Michelangelo Mancuso[1]

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Table 1 Phenotype

Phenotype	Predominant phenotype at baseline: number of patients (%)	Patients with this movement disorder as secondary features at onset	Patients developing this movement disorder later during the course of the disease	Cumulative prevalence at follow-up. Number of patients (%)
Ataxia	55 (53.9)	0	7	62 (59.1)
Hypokinetic	26 (24.8)	0	6	32 (30.5)
Myoclonus	13 (12.3)	6	3	22 (20.9)
Hyperkinetic	11 (10.5)	3	2	16 (15.3)

Prevalence of phenotype at baseline and last follow-up: percentages refers to proportions within the 105 patients who have a mitochondrial movement disorders

Disordini del movimento

105/764 pazienti con PMD con mioclono, ataxia e disrdini del movimento erano parte del fanotipo clinico all'interno del registro clinico.

Table 3 Genotype–phenotype correlation

	Movement disorders: yes ($n=105$)	Movement disorders: no ($n=659$)	
m.3243A > G pathogenic variant	8 (7.6%)	47 (7.1%)	n.s.
m.8344A > G pathogenic variant	17 (16.2%)	16 (2.4%)	**< 0.0001**
mtDNA LHON pathogenic variants	1 (0.9%)	154 (23.4%)	**< 0.0001**
mtDNA single deletion	9 (8.6%)	125 (19.0%)	**0.003**
nDNA: *OPA1* pathogenic variants	4 (3.8%)	25 (3.8%)	n.s.
nDNA: *POLG* pathogenic variants	23 (21.9%)	19 (2.9%)	**< 0.0001**
nDNA: *Twinkle* pathogenic variants	7 (6.7%)	23 (3.5%)	n.s.

The patients have been divided in two groups, with and without movement disorders. Genotypes with less than 25 patients have not been considered and are not shown. Significance levels after Bonferroni's correction 0.007. Significant differences are represented in bold

n.s. not significant

of patients with movement disorders

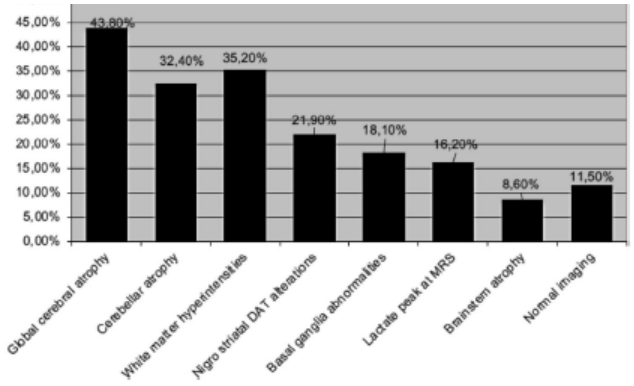
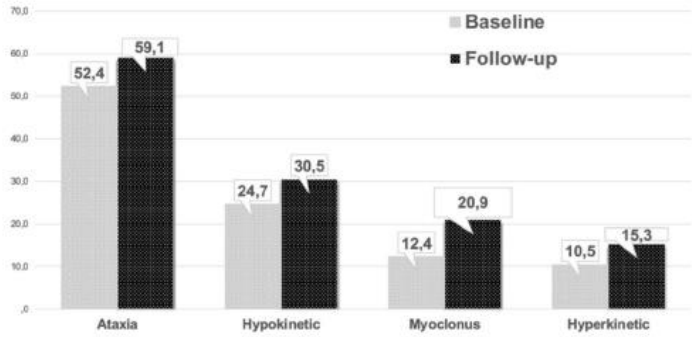


Fig. 1 Prevalence of movement disorder phenotypes at baseline and last follow-up: percentages refers to proportions within the 105 patients who have a mitochondrial movement disorders



LEUCOENCEPHALOPATHY

1) Sindromi mitocondriali «KSS/MELAS/MERRF/MINGIE

2) «alterazioni classiche dell'OXPHOS

gene	fenotipo
MELAS	Miopathy Stroke like episodes, diabetis, eraing loss
MERRF	Miyopcolono epilepsy , RRF fibers
KSS	Short stature , leucoencephalopaty, earing loss , aritmya
MNGIE	

Qualitative and quantitative alteration of mtDNA

3)Malattie mitocondriali secondarie ad alterazioni della sintesi degli aminoacidi

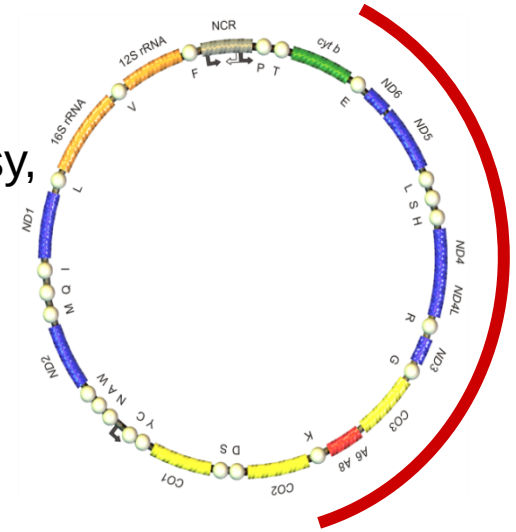
4) Sindrome da disfunzione mitocondriale multiple (MMDS) da difetto delle proteine del cluster Ferro-Zolfo

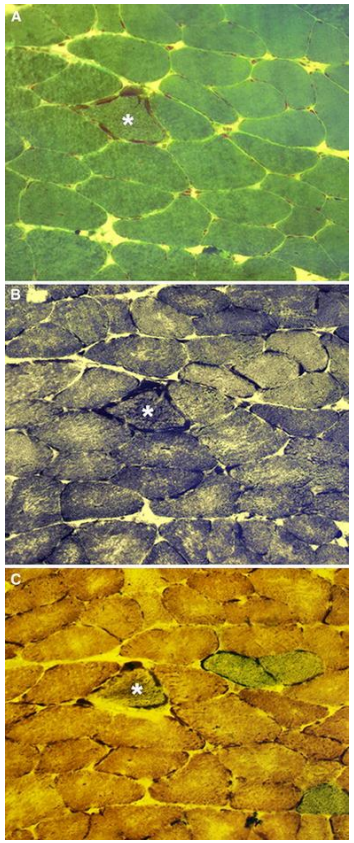
gene	fenotipo
DARS2	Leucoencefalopatia con coinvolgimento TE e mid spinale, aumento lattato (LBSL)
EARS2	Leucoencefalopatia con coinvolgimento talamo e TE, aumento lattato (LTBL)
AARS2	CMI/leucodistrofia
MARS2	Leucoencefalopatia, sdr atasso-spastica (ARSAL)

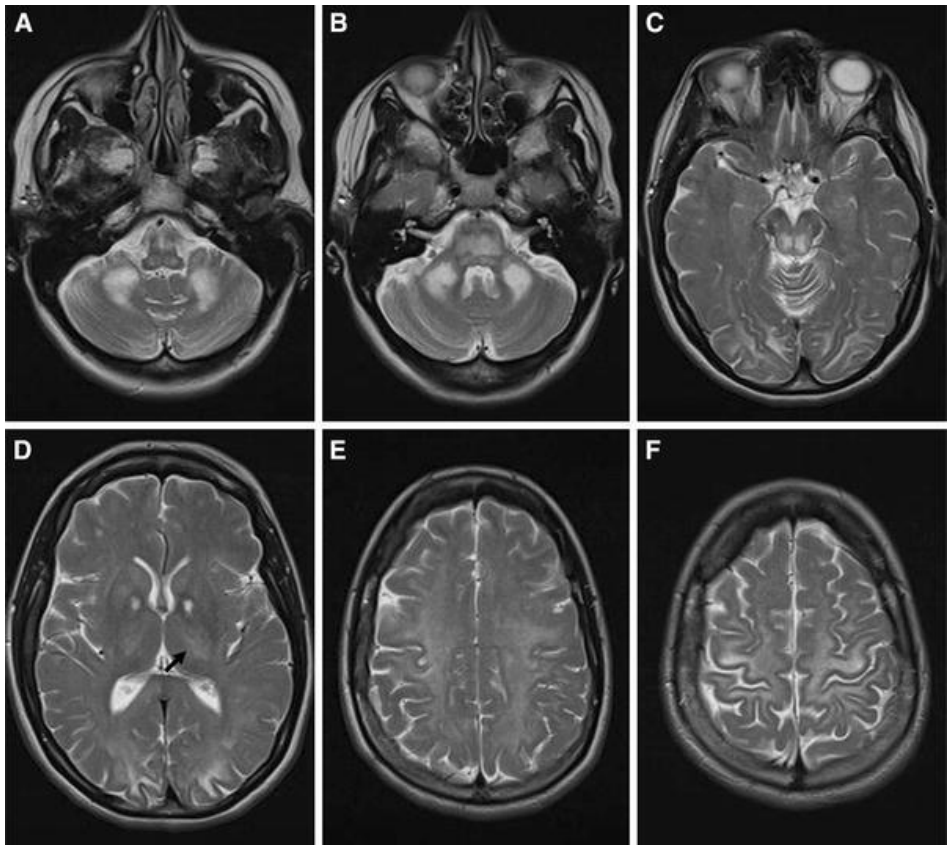
compl. I-III-IV deficinecy o normal

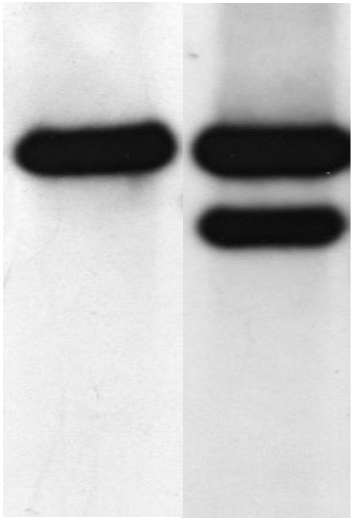
KSS

PEO , arithmia leucoencehalopathy, dementia, deafness, epilepsy, Short stature

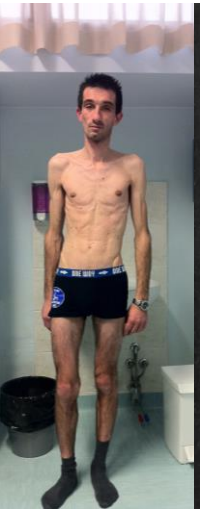
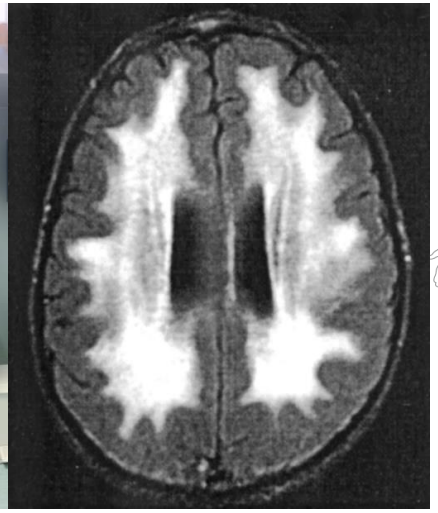
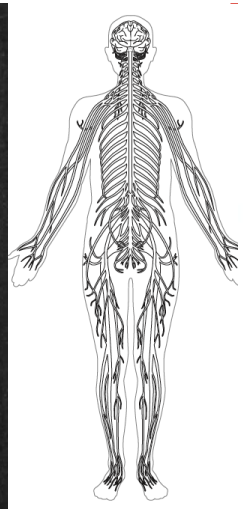
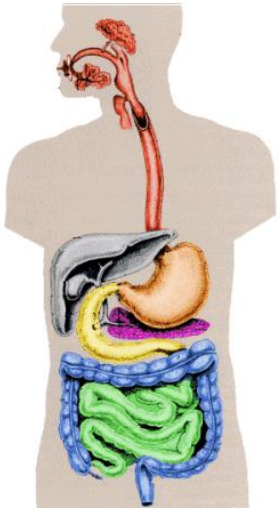
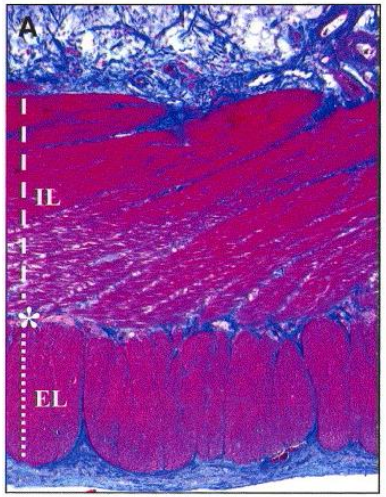


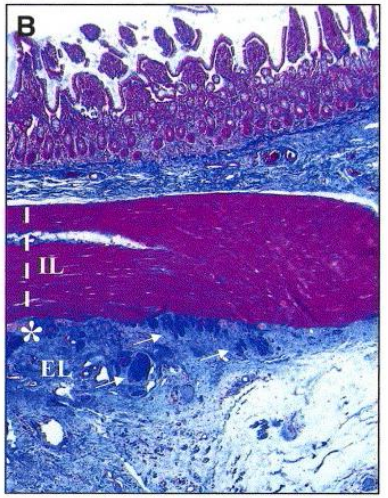






MNGIE

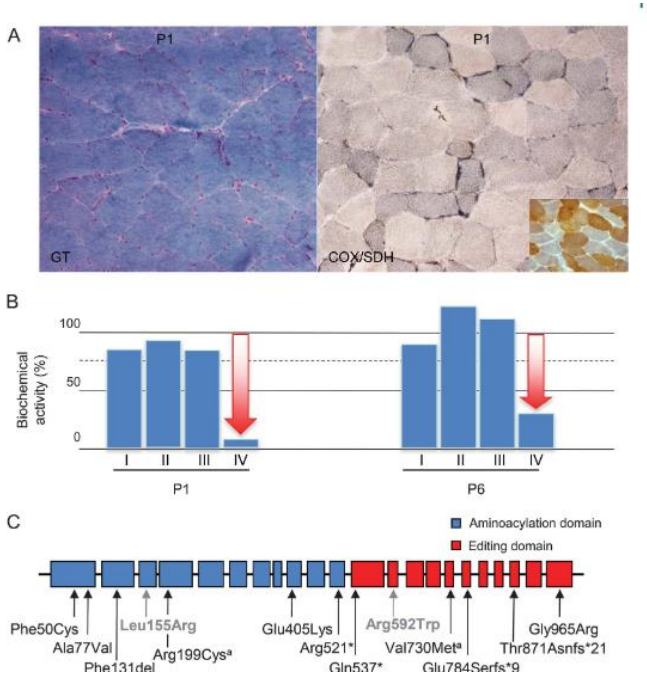


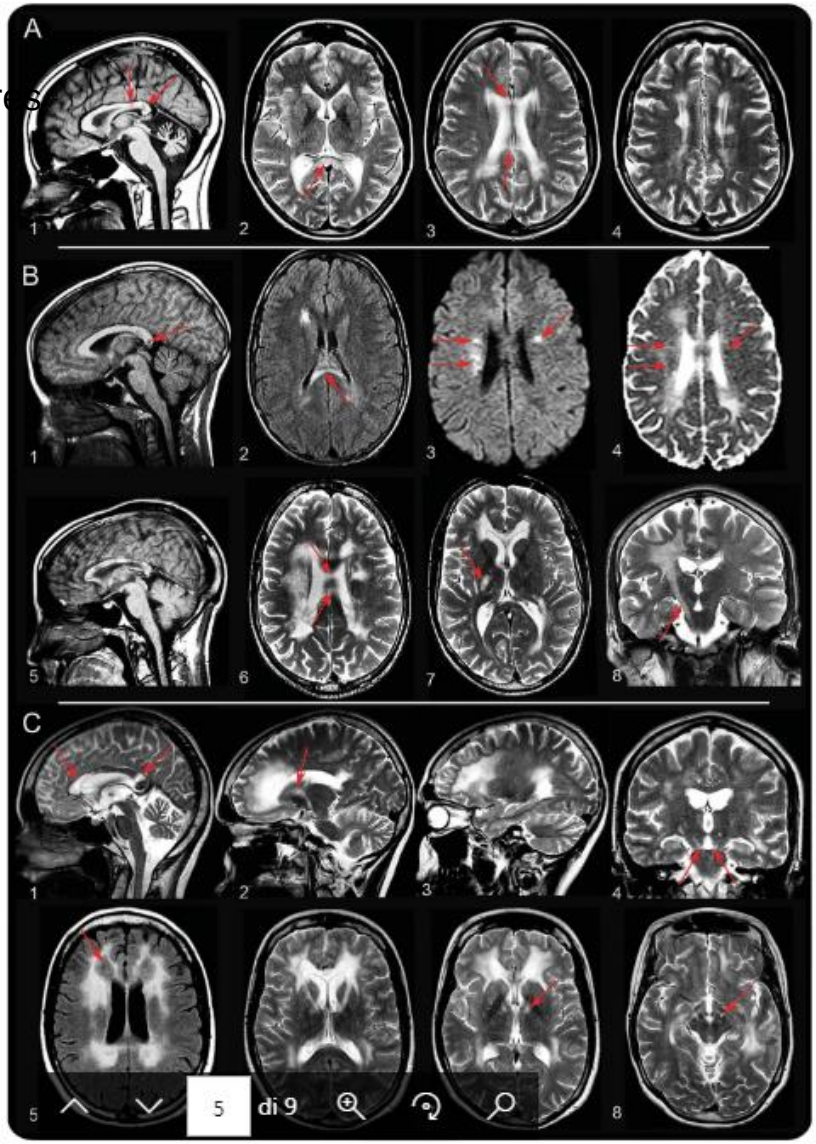
- Myo-neuro-gastro-intestinal encephalomyopathy
- Autosomal recessive
- Combined mtDNA depletion, deletions
- Due to mutations in thymidine phosphorylase

AARS 2

Childhood to adulthood-onset signs of neurologic deterioration consisting of ataxia, spasticity, and cognitive decline with feature of frontal lobe dysfunction.

MRIs showed a leukoencephalopathy with striking involvement of left-right connections, descending tracts, and cerebellar atrophy





Della Bona C , Diodato D et al 2014

Leucoencephalopathy LBSL/*DARS2*

Alteration in the white metter alterazioni di segnale (iper in T2, ipo in T1):

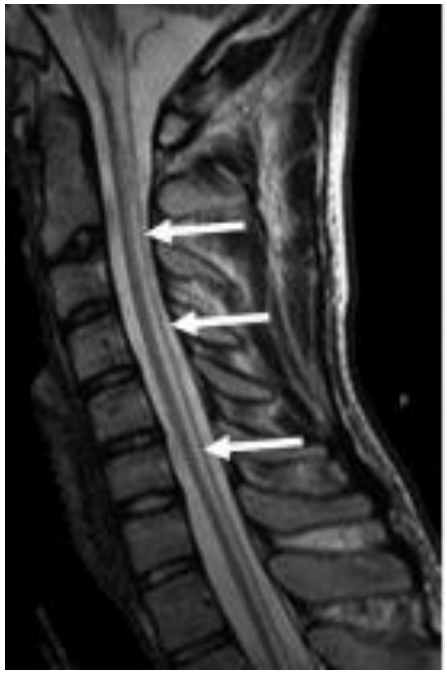
- diffuse della SB con relativo risparmio delle fibre a U
- a livello **dei fasci cortico-spinali laterali e dei colonne dorsali del midollo spinale** , delle piramidi a livello del bulbo

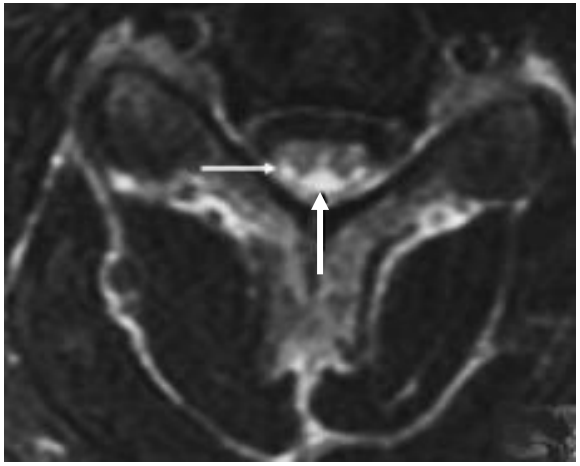
Criteri di supporto:

➢ alterazioni di segnale (iper in T2, ipo in T1):

- Splenio del corpo calloso
- Braccio posteriore della capsula interna
- Lemnisco mediale del TE
- Peduncoli cerebellari superiori/inferiori
- Tratto intraparenchimale/mesencefalico del nervo trigemino
- Tratto spino-cerebellare anteriore del bulbo
- SB cerebellare con prevalenza sottocorticale

➢ Picco di lattato a livello della alterazioni della SB (MRS)





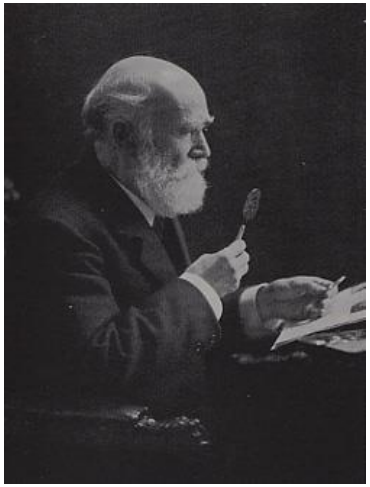
Hart involvement

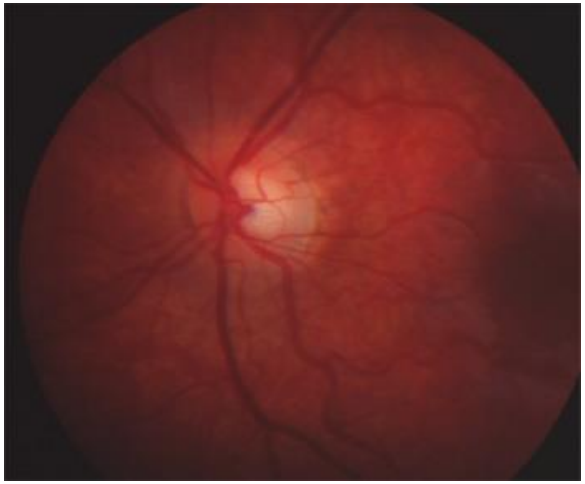
- Dilative cardiomyopathy
- Hypertrophyc cardiomyopathy
- Bradycardia
- BAV
- Heart falure

Sympthoms: absent since a very late stage of the diseases

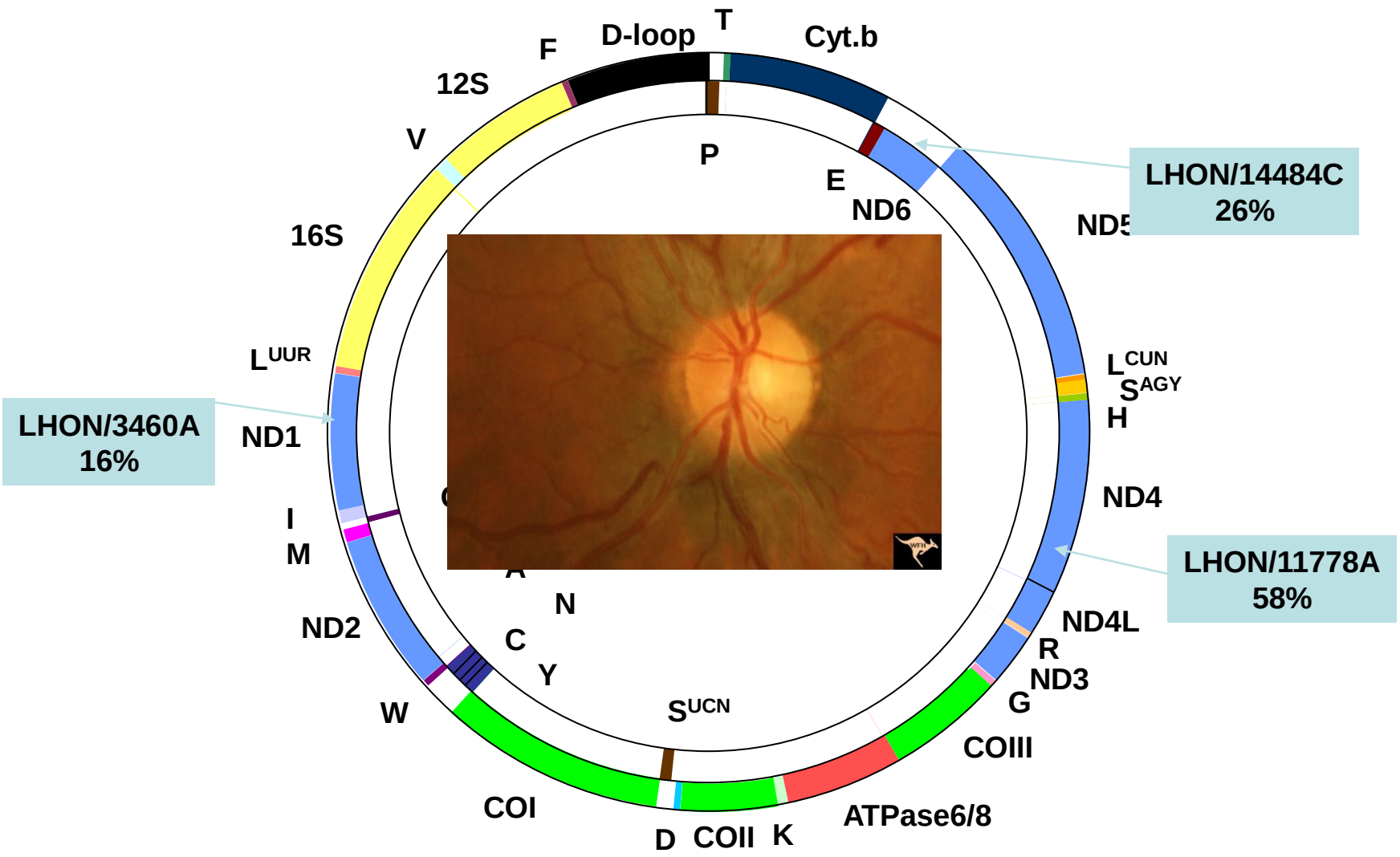
Leber's Hereditary Optic Neuropathy (LHON)

Leber, T. : Ueber hereditaere und congenital angelegte Sehnervenleiden. Graefes Arch. Ophthal. 17: 249-291, 1871.





Onset symptom: a painless, sub-acute, central visual loss in one eye, progressively spreading to the opposite, in weeks or months.



Unica forma di malattia da mutazione del mt DNA che da una patologia monorgano pur essendo presente la mutazione i tutti i tessuto

Approccio multidisciplinare

Prevista **invalidità civile** (età adulta)
Prevista **indennità integrativa** (età pediatrica)
Esenzione da utilizzare nel processo diagnostico
In caso vi fosse un sospetto diagnostico di malattia di MERRF o MELAS sulla base dei criteri menzionati nel presente documento, le indagini diagnostiche potranno essere effettuate utilizzando **il codice di esenzione R99**, che corrisponde al codice di sospetta malattia rara.
Esenzione dopo l'accertamento della diagnosi: **RN0720 d RN0730 a RF0030 RF0300 utilizzare per il certificato di malattia rara** e per il piano terapeutico annuale. Tale codice serve al malato per avere gratuitamente esami utili nel follow-up clinico, biochimico estrumentale e per i farmaci relativi alla patologia di base elencati nel piano terapeutico di ogni paziente.
Provvedimenti **Legge 104/1992** per frequenti visite di controllo, trattamenti riabilitativi e terapeutici**.**

RegioneLombardia
Centro di Coordinamento della Rete Regionale per le Malattie Rare

http://malattierare.marionegri.it/

Monitoraggio

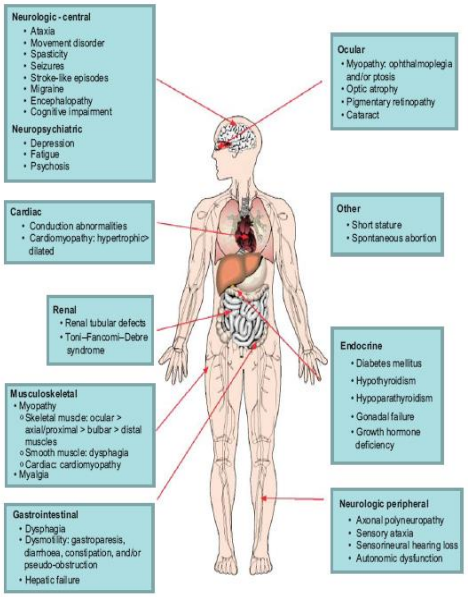


Figure 1. Clinical features of mitochondrial myopathies, by organ system.

Esame/Procedura	*Indicazioni*
ECG, ecocardiogramma	Monitoraggio della funzionalità cardiaca e prevenzione delle possibili complicanze.
ECG-Holter	Individuazione e monitoraggio del ritmo cardiaco.
Esame audiometrico	Monitoraggio della sordità ed eventuale controllo di protesi ad hoc.
Spirometria	Monitoraggio della funzionalità respiratoria, soprattutto nelle fasi terminali di malattia.
Esami ematochimici	Glicemia, emoglobina glicata, funzionalità tiroidea.
Poligrafia EEG	Monitoraggio della sintomatologia epilettica.

Visita specialistica	*Indicazioni*
Neurologo / neuropsichiatra infantile	Valutazione clinica dell'evoluzione della malattia e supporto nel caso di eventi acuti (crisi metabolica).
Endocrinologo	Monitoraggio del diabete ed eventualmente di altri disturbi endocrinologici spesso associati (patologia tiroidea, disturbi degli ormoni sessuali).
Cardiologo	Valutazione monitoraggio della patologia cardiaca e modificazione della terapia o indicazioni ad eventuali interventi.
Fisiatra	Valutazione fisiatrica ed eventuale stesura del PRI (Progetto Riabilitativo Individuale) allo scopo di ridurre l'inabilità e prevenire le complicanze legate alle difficoltà motorie.
Neuroftalmologo	Monitoraggio della patologia oculistica, in particolare del grado di difetto visivo sia a carico del nervo ottico che della retina.
Otorinolaringoiatra	Valutazione della eventuale sordità e posizionamento di eventuali protesi acustiche. Eventuale monitoraggio dell'insorgenza di una possibile disfagia che può presentarsi nel tempo.

Non esistono terapie curative per le malattie mitocondriali

…….**Tuttavia**……..

Terapia sintomatica :

•Infusione intravenosa in fase acuta di L-arginina

•CoQ10

Idebenone

•antiepilettici(non acido valproico, valium Keppra),

•terapia miorilassante(lyoresal, pompa al baclofen)

•Terapia cardiologica

•Terapia dibetica

•FKT e training

Amsterdam 1st and 2nd of November

POTENTIALLY HARMFUL DRUGS FOR MITOCHONDRIAL PATIENTS

Maaike C. De Vries
Mitchell E. Allen
Laurence Bindoff
David A. Brown
Gráinne S Gorman
Amel Karaa
Nandaki Keshavan
Costanza Lamperti
Michelangelo Mancuso
Robert McFarland
Yi Ng
Kristin N. Varhaug
Mar O'Callaghan
Robert D.S. Pitceathly
Shamima Rahman
Frans Russel
Tom Schirris

The entire workshop was sponsored by patient organisations: AEPMI, DGM, Eurordis, IMP, the Lily Foundation, MitoCanada, Mitocon and Muscular Dystrophy UK

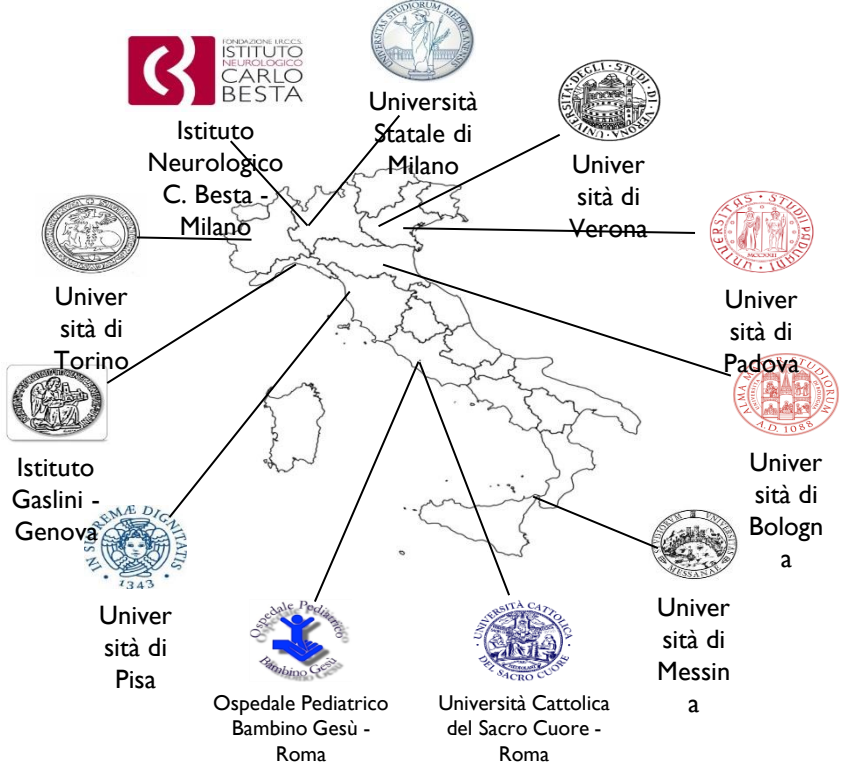
Trial

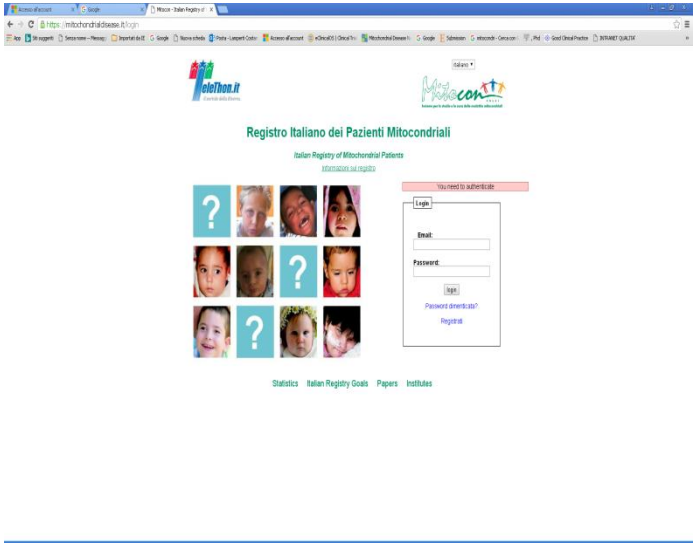
- Elamipretide in primary mitocondrial disease
- Gene therapy in LHON,
- Gene therapy for MNGIE
- Idebenone in LHON
- KH176 for MELAS.
- Elamipretide SPIMM301/302
- RENEO 001

https://clinicaltrials.gov/

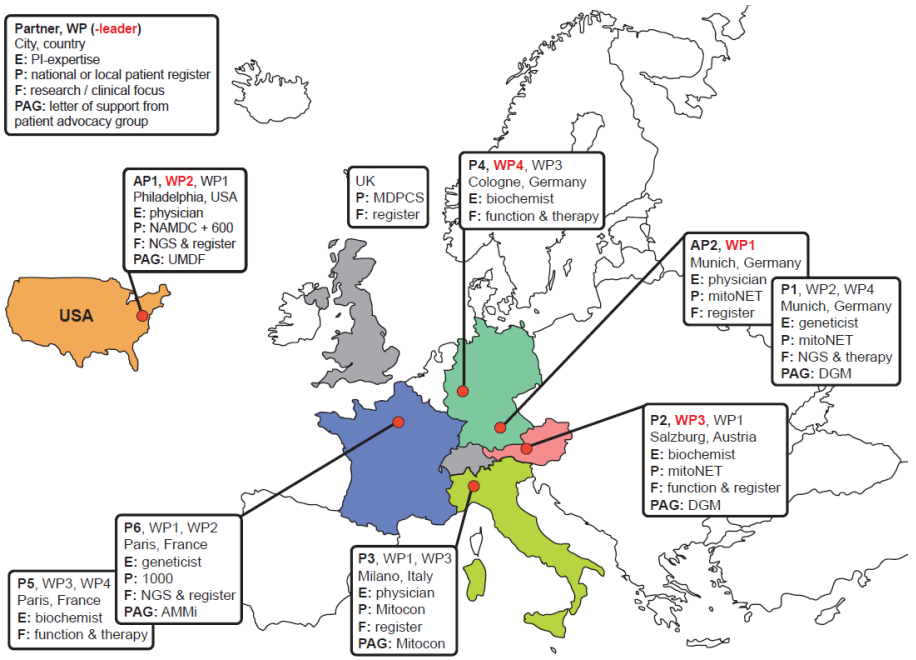
594 studies found for: mitochondrial diesease.

La maggior parte di tipo osservazionali di storia naturale


Istituto Neurologico C. Besta - Milano
Università Statale di Milano
Univer sità di Verona
Univer sità di Torino
Univer sità di Padova
Istituto Gaslini - Genova
Univer sità di Bologn a
Univer sità di Pisa
Univer sità di Messin a
Ospedale Pediatrico Bambino Gesù - Roma
Università Cattolica del Sacro Cuore - Roma


Registro Italiano dei Pazienti Mitocondriali
Italian Registry of Mitochondrial Patients
Statistics
Italian Registry Goals
Papers
Institutes

GENOMIT


Partner, WP (-leader)
City, country
E: PI-expertise
P: national or local patient register
F: research / clinical focus
PAG: letter of support from patient advocacy group
AP1, WP2, WP1
Philadelphia, USA
E: physician
P: NAMDC + 600
F: NGS & register
PAG: UMDF
USA
UK
P: MDPCS
F: register
P4, WP4, WP3
Cologne, Germany
E: biochemist
F: function & therapy
AP2, WP1
Munich, Germany
E: physician
P: mitoNET
F: register
P1, WP2, WP4
Munich, Germany
E: geneticist
P: mitoNET
F: NGS & therapy
PAG: DGM
P2, WP3, WP1
Salzburg, Austria
E: biochemist
P: mitoNET
F: function & register
PAG: DGM
P6, WP1, WP2
Paris, France
E: geneticist
P: 1000
F: NGS & register
PAG: AMMi
P5, WP3, WP4
Paris, France
E: biochemist
F: function & therapy
P3, WP1, WP3
Milano, Italy
E: physician
P: Mitocon
F: register
PAG: Mitocon

Sistema Socio Sanitario

Fondazione I.R.C.C.S.
Istituto Neurologico Carlo Besta

Regione Lombardia

UO Genentica Medica e Neurogenetica

Barbara Garavaglia
Valeria Tiranti
Daniele Ghezzi
Eleonora Lamantea
Federica Invernizzi
Silvia Marchet
Alessia Catania
Ivano Di Meo
Andrea Legati
Nadia Zanetti
Manuela Spagnolo
Alessia Nasca
Daniele Sala
Krisztina Eveing

UO Neuropsichiatria Infantile

Isabella Moroni
Anna Ardissone

Helmholtz Zentrum München

Holger Prokisch
Sarah Steanton
Dimitrii Smirnov
Aiman Farzeen

UO Neurologia IV

Lorenzo Maggi
Silvia Bonanno
Blavia Blasevic
Franco Salerno

LMU Klinikum München

Thomas Klopstok
Boriana Buechner

European Reference Networks

Ministero della Salute

Fondazione
Pierfranco e Luisa Mariani
ONLUS
neurologia infantile

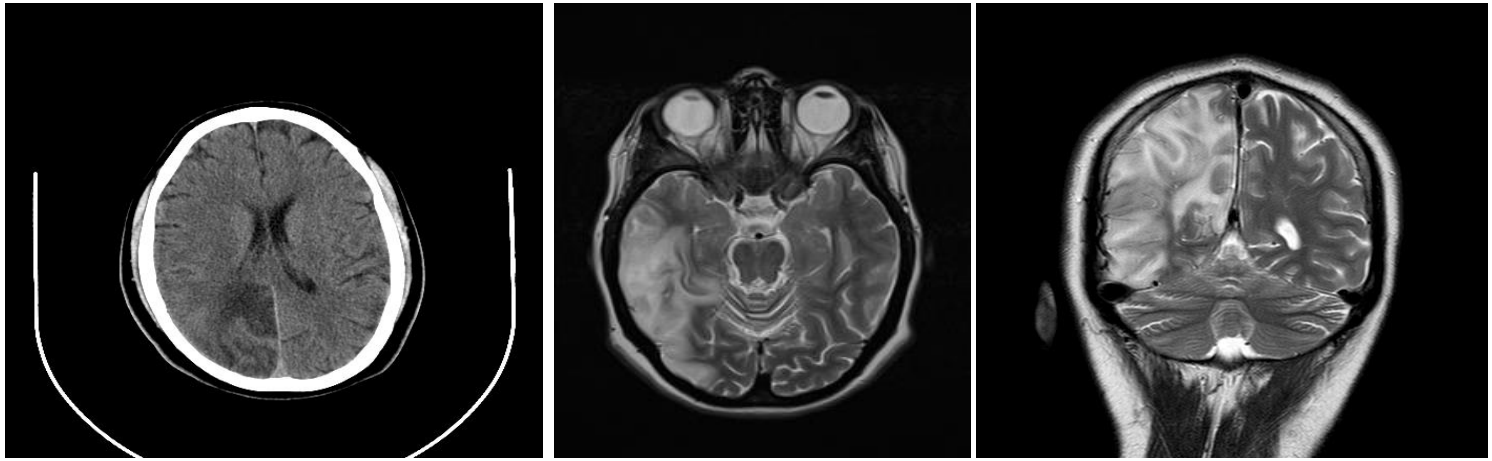
Mitocon
Insieme per lo studio e la cura
delle malattie mitocondriali

E-Rare

Risultati

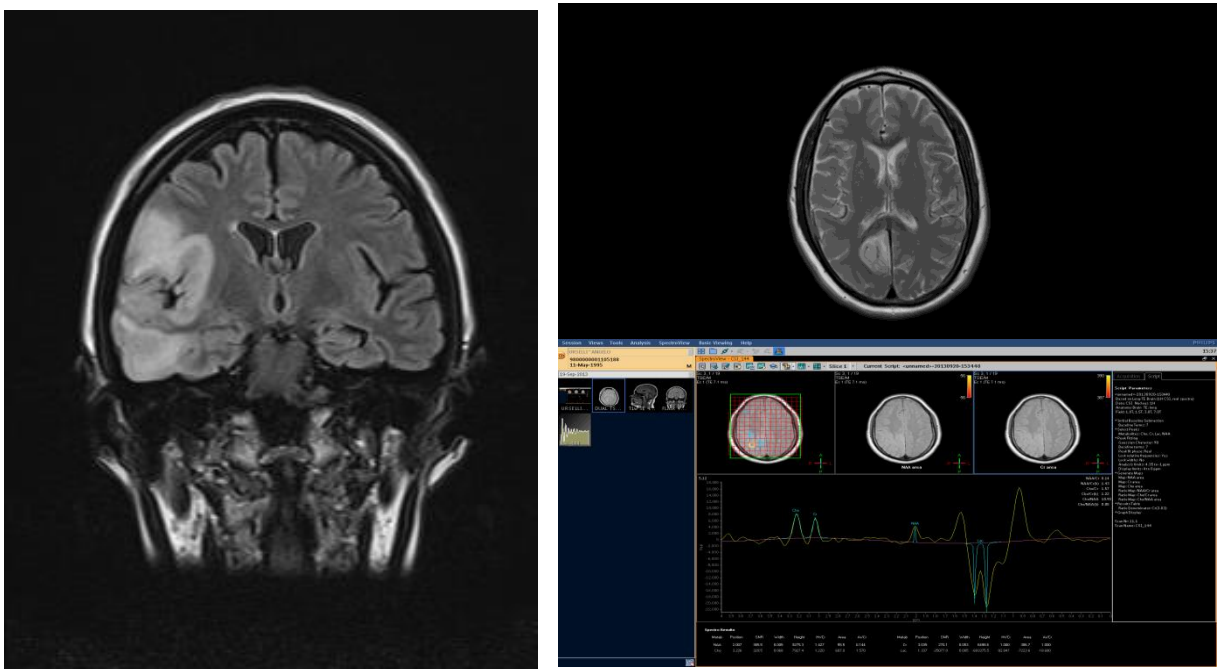
QUESTION	MEAN	% OF PEOPLE VOTING 4 OR	CONSENSUS
VALPROIC ACID SHOULD BE AVOIDED ONLY IN POLG PATIENTS	4,25	81,25	STRONG
IN NON-POLG PATIENTS WITH MITOCHONDRIAL DISEASE, WITHOUT LIVER DISEASE, VALPROIC ACID COULD BE USED TO MANAGE REFRACTORY EPILEPSY AND REFRACTORY MOOD DISORDERS	4,4	100	STRONG
AS A GENERAL APPROACH, SHORT TERM (< 7 DAYS) ANTIBIOTIC TREATMENT IS UNLIKELY TO BE A PROBLEM IN PMD. INFECTION IS A MUCH GREATER RISK THAN SHORT TERM ANTIBIOTICS	4,75	100	STRONG

Neuroimmagine : MELAS

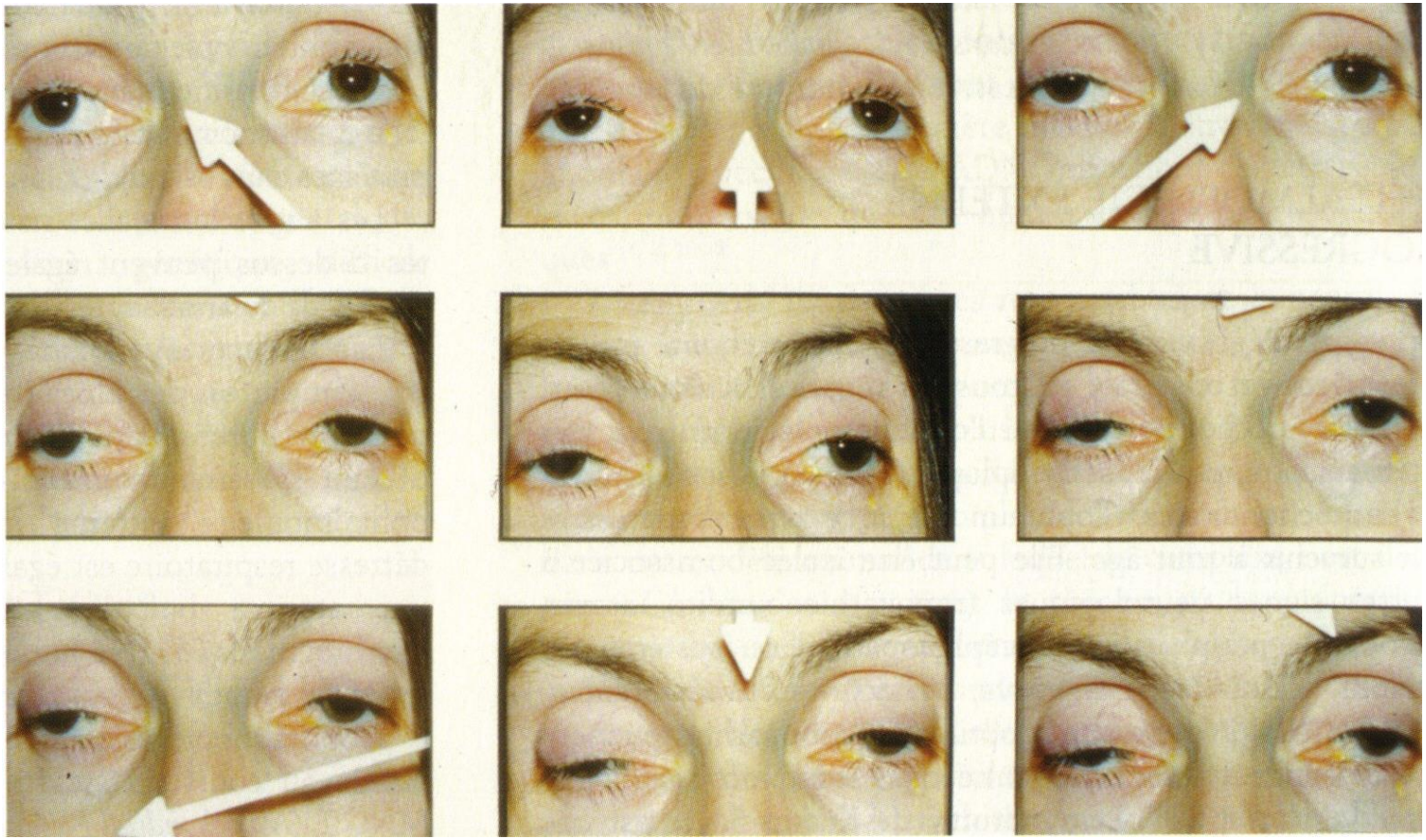


PZ1

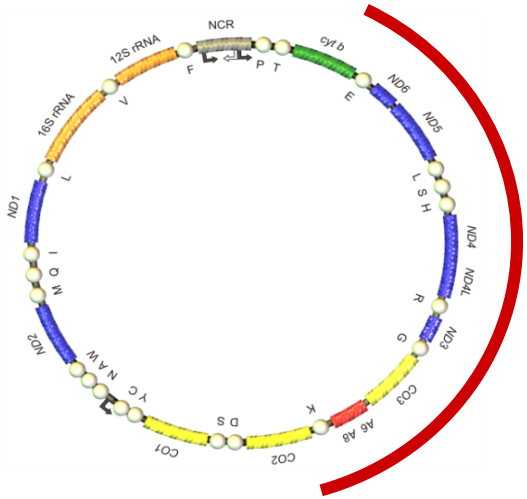
PZ2

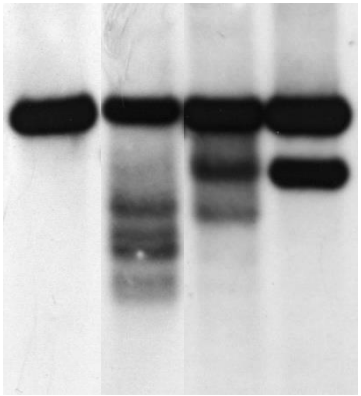


PEO



Difetti nelle proteine coinvolte nel mantenimento e nella replicazione del mtDNA (Difetti multipli della catena respiratoria)



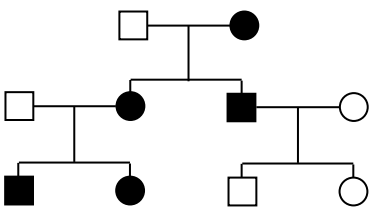


Delezioni multiple (alterazione qualitativa)

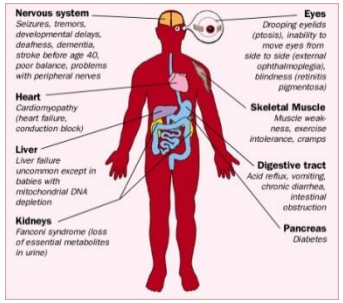
Gene	Forma
TYMP	MNGIE
TK2	Miopatica
DGUOK	Epatocerebrale
POLG1	sindrome di Alpers MNGIE
SUCLA2	Encefalomiopatia con Aciduria Metilmalonica
MPV17	Epatocerebrale
C10orf2 (Twinkle)	Epatocerebrale
RRM2B	Encefalomiopatia e tubulopatia MNGIE
SUCLG1	Encefalomiopatia con Aciduria Metilmalonica

Gene	Forma
TYMP	MNGIE
SLC25A4	AD PEO
C10orf2 (Twinkle)	AD PEO
POLG1	AD PEO AR PEO
POLG2	AD PEO
RRM2B	AD PEO
OPA1	AD Atrofia ottica, Sordità, Oftalmoplegia,
TK2	AR PEO
DGUOK	AR PEO

Percorso diagnostico

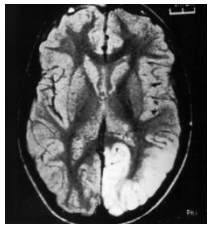


Valutazione clinica approfondita



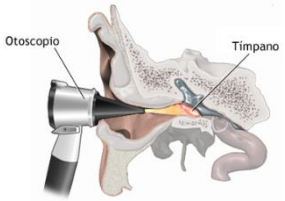
Storia famigliare

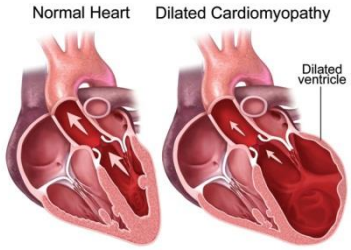
Indagini neuroradiologiche



Valutazione neuroftalmologica

Valutazione audiologica

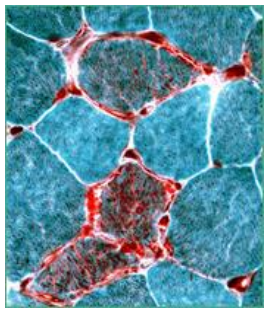


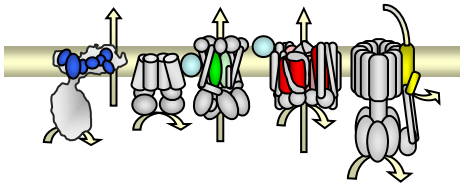


Valutazione cardiologica

Valutazione neurofisiologica

Biopsia muscolare



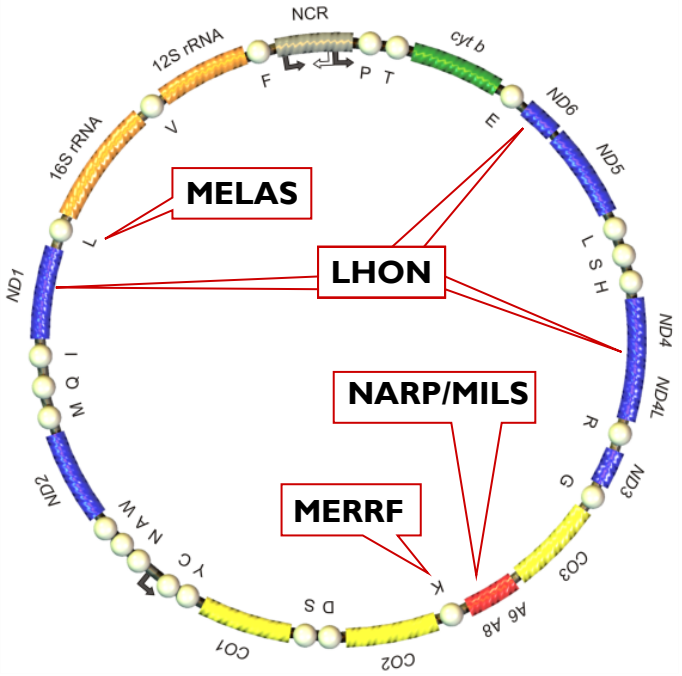


Indagini biochimiche
e molecolari

Indagini Iniziali e di Approfondimento

- **Lattato e piruvato** a riposo e sotto sforzo standardizzato (L/P > 20 RCD, difetti Krebs; < 10 difetto PDC) (L/P = misura stato redox citopl.)
- Dosaggio CPK
- FGF21

Mutazioni del mtDNA



1988: prima mutazione del mtDNA.

Oggi più di 200 mutazioni descritte, sei le più frequenti:

- m.3460G>A *ND1*
- m.11778G>A *ND4*
- m.14484T>C *ND6*
- m.3243A>G *tRNA^{L}*
- m.8344A>G *tRNA^{K}*
- m.8993T>G *ATP6*

LHON: atrofia ottica bilaterale, esordio acuto.

MELAS: emicrania, stroke-like, acidosi lattica, demenza, atassia, epilessia, miopatia, diabete, sordità, bassa statura.

MERRF: epilessia mioclonica, miopatia, atassia, atrofia ottica, sordità, demenza, cardiopatia, lipomatosi.

NARP: neuropatia, retinite pigmentosa, atassia, debolezza muscolare, ritardo sviluppo, epilessia, demenza.

MILS: sindrome di Leigh matrilineare, ritardo sviluppo, epilessia, dismorfismi, miopatia.

MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, Stroke)

- **Esordio :** Media 20 anni (dai 2 ai 40 anni)
- **Sindrome clinica**: episodi stroke like, emicrania, vomito,sordita' occasionalmente crisi convulsive, decadimeto congitivo, diabete, miopatia bassa statura, magrezza
- **RMN encefalo** : lesioni cerebrali, picco di lattato alla spettroscopia.
- **Esami di lab**: lattato elevato, CPK elevate ma anche normali.

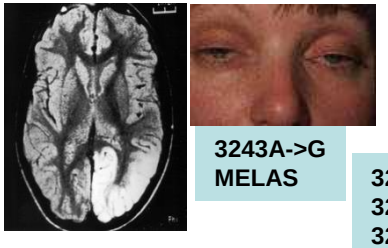
Biopsia muscolare

Ragged red fibers (RRF):

COX **+**; SDH **+,** RRF:COX-

Terapia

Durante la crisi metabolica acuta, che si può manifestare sia come episodio deficitario (episodio stroke-like) o come crisi epilettiche subentrati, o episodi di vomito profuso e stato confusionale, viene considerata utile la terapia con **l-arginina ev al dosaggio di 0.4-0,5 g/kg.** A tale terapia, in fase di risoluzione dell'evento acuto si può proseguire con dosaggio inferiore per circa 4 settimane.
In caso di crisi epilettiche subentranti, è necessario adottare le misure che vengono utilizzate per gli stati di male. Se necessario, la terapia con bicarbonato di sodio corregge l'eventuale acidosi metabolica. Inoltre il paziente necessita di tutti i supporti del caso (ad es. eventuale supporto respiratorio) e deve essere seguito in regime di ricovero in una terapia intensiva sotto stretto monitoraggio.



3243A->G
MELAS

3241T->C
3243A->G
3250T->C
3251A->G
3252A->G
3254C->G
3260A->G
3264T->C
3271T->C
3271ΔT
3288A->G
3291T->C
3302A->G
3303C->T

1555A->G

583G->A
606A->G
618T->C

1606G->A
1642G->A
1644G->T

15915G->A
15293A->G

14787Δ4bp
14846G->A
15243G->A
15244G->A
15059G->A
15084G->A
15168G->A
15257G->A
15498G->A
15498Δ24bp
15615G->A
15723G->A
15762G->A
15812G->A

12311T->C
12315G->A
12320A->G
12301G->A

15990C->T

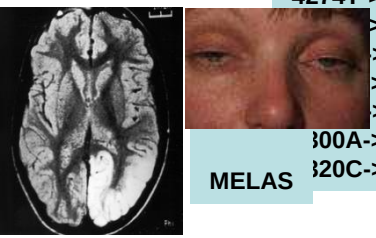
14709T->C

13513G->A
13514A->G

14484T->C
14459G->A

3460G->A
7bp inversion

4269A->G
4274T->C
>C
>A
>G
>A
300A->G
320C->T



MELAS

4409T->C

7445A->G
7511T->C
7472C$_{ins}$

5692A->G
5703G->A

5814A->G

11778G->A
11832G->A

15bp deletion
9537C$_{ins}$
9957T->C

9997T->C
10044A->G

5521G->A
5537T$_{ins}$
5540G->A
5549G->A

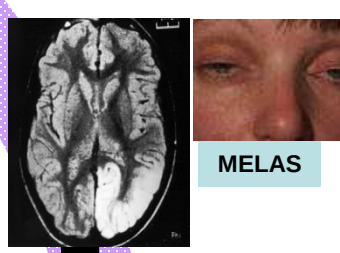
5bp deletion
6930G->A

7543G->A

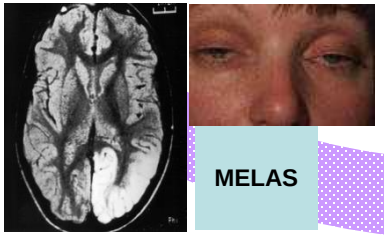
7671T->A

8313G->A
8328G->A
8342G->A
8344A->G
8356T->C
8363G->A
8296A->G

8851T->C
8993T->G
8993T->C
9176T->C
9176T->G



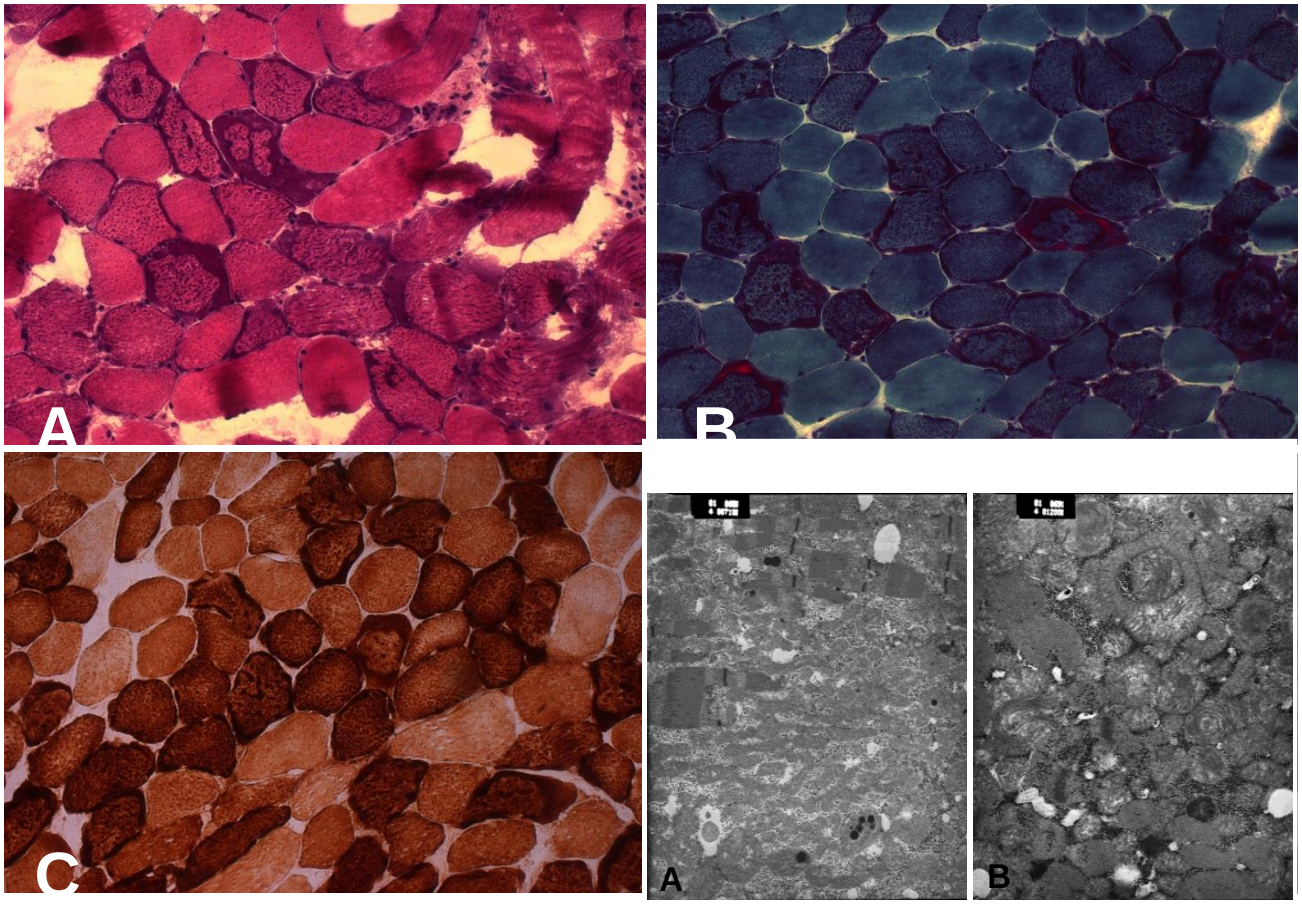
MELAS



MELAS

D-loop
12S
16S
Cyt.b
ND1
ND2
ND3
ND4
ND4L
ND5
ND6
COI
COII
COIII
ATPase6/8
F
V
L^{UUR}
I
Q
M
A
N
C
Y
W
S^{UCN}
D
K
T
P
E
L^{CUN}
S^{AGY}
H
R
G

DISEASE



mtND2

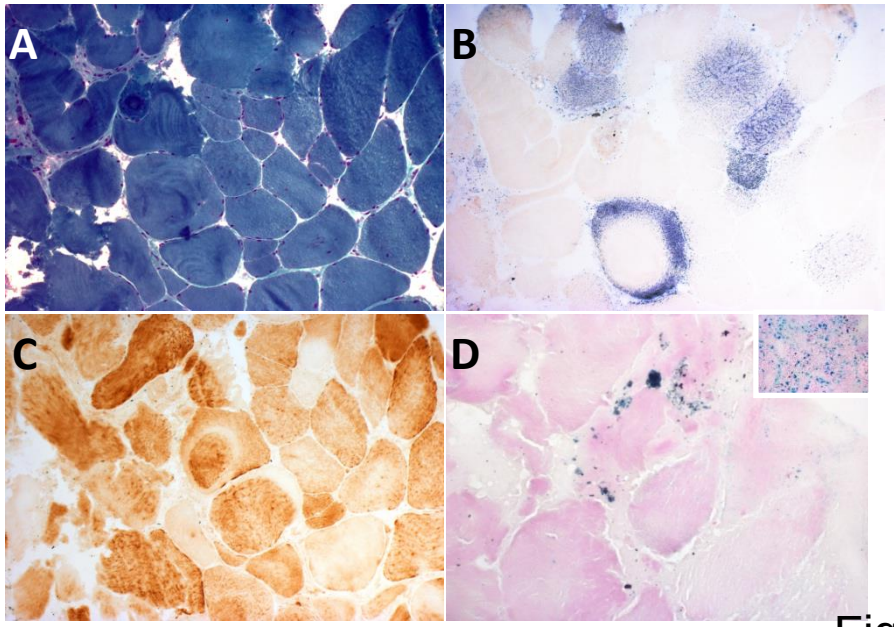
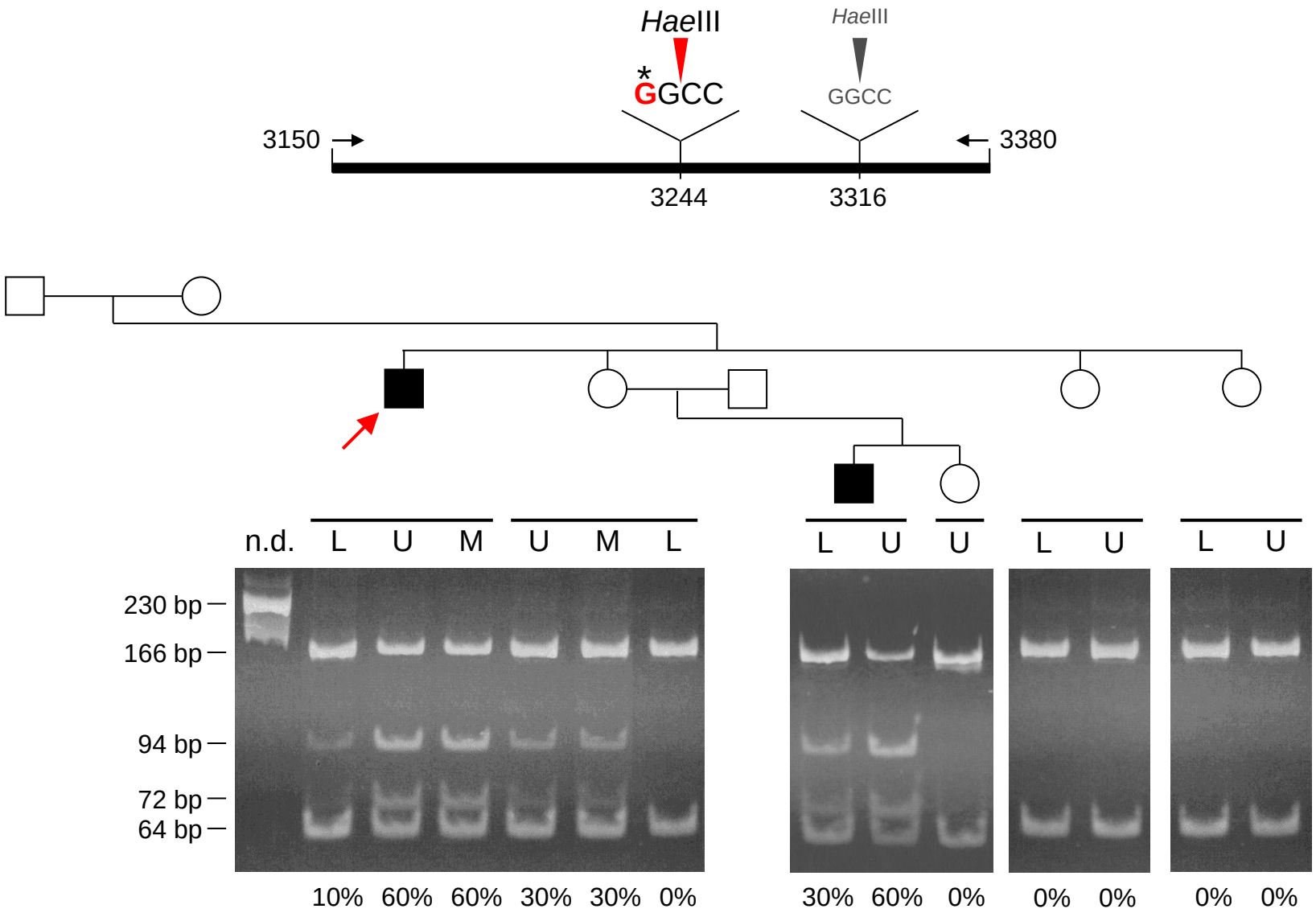


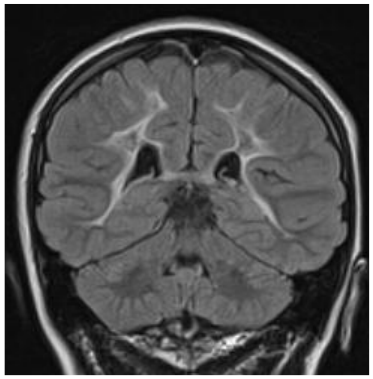
Fig. 1

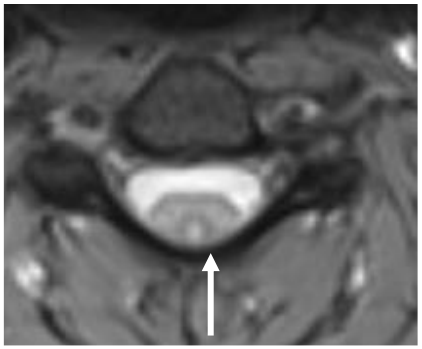
ISCU

RFLP Analysis: *Hae*III Enzyme

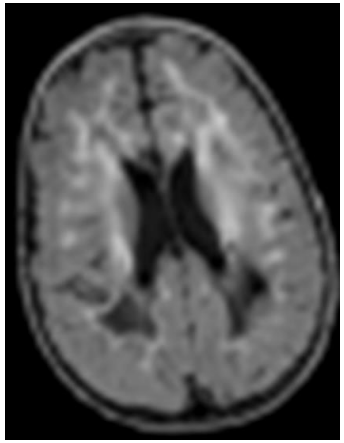


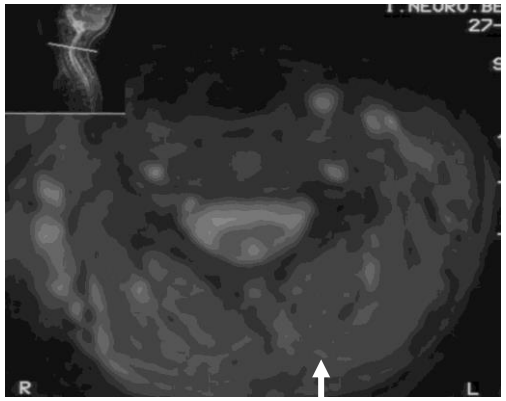
Leucoencephalopathy MMDS/*IBA57*





M.M.
dif compl I muscolo
(n fibroblasti)





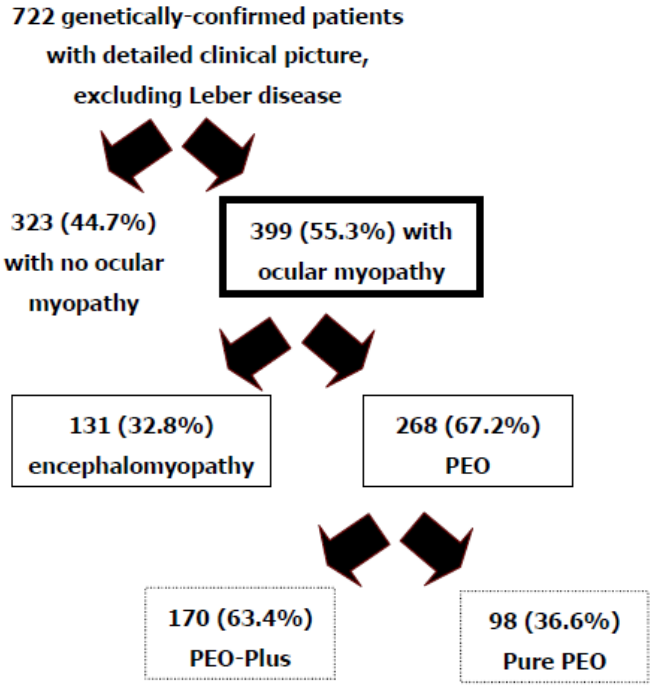
G.M.
dif compl II

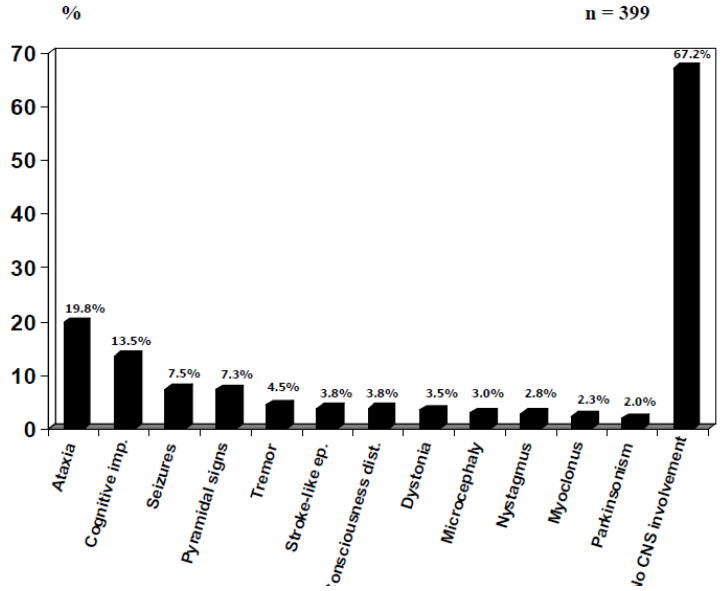
Una sindrome tanti geni …

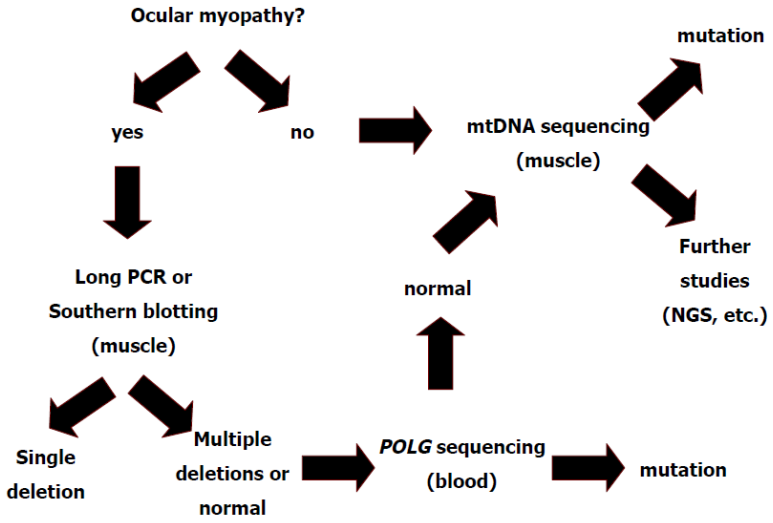
- Riarrangiamento dell'mtDNA : macrodelezioni/ delezioni mulitple
- Geni nucleare (POLG1,TWINKLE, RNASIH, DGUK; TK2, RRM2B) …..
- Mutazioni singole dell'mtDNA
- Eziologia ignota

…….Diversa ereditarieta'

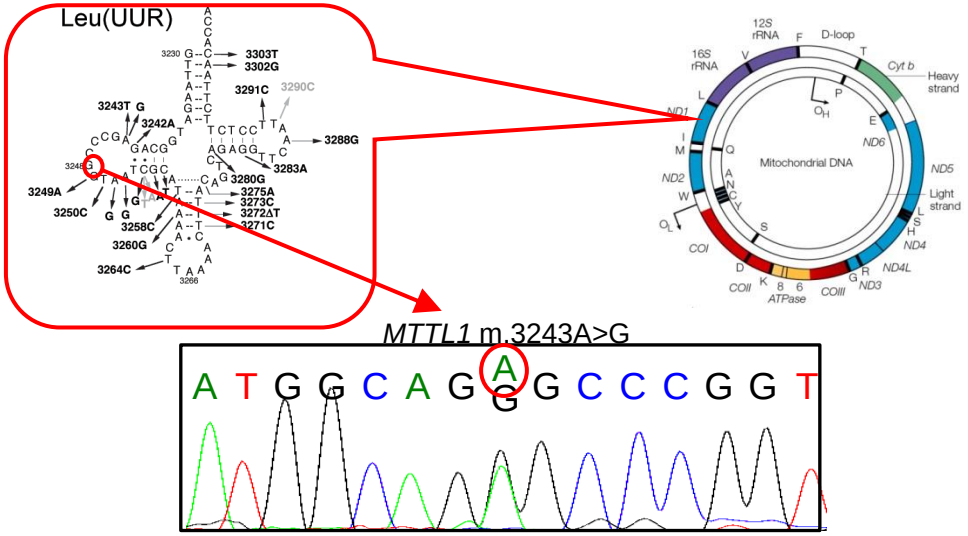
Revisiting Mitochondrial Ocular Myopathies: A Study from the Italian Network.





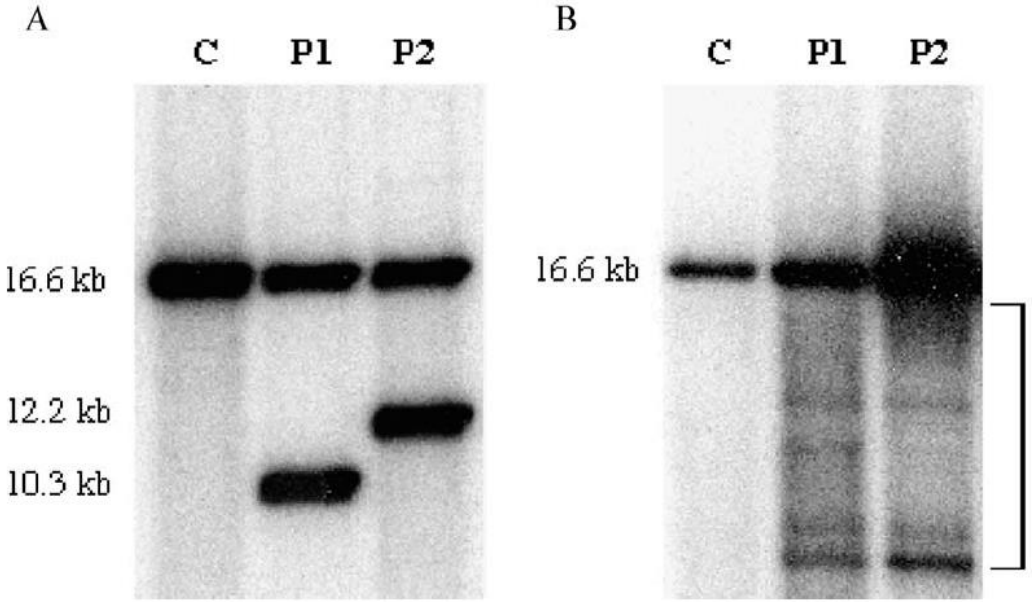


Analisi Molecolare



MTTL1 m.3243A>G

Sequenziamto mtDNA



SB-mtDNA

International Workshop on Trial readiness in primary mitochondrial myopathies PMM

Rome, 16th-18th November 2016

Organized by:

M.Hirano, T. Klopstock, M.Mancuso and R. McFarland

Sponsored by:

IMP, AEPMI, AMMI, Mitocon Onlus and UMDF

26 researchers from 10 different countries (USA, Spain, Italy, France, Germany, The Netherlands, United Kingdom, Japan, Norway, Canada)

International Workshop on trial readiness in primary mitochondrial myopathies

Ideas for hunting down the right path to a cure

Novembre 2016

NMDAS
Hammersmith Functional Motor Scale Expanded
Short Form 36 Health Survey (SF-36) score
Myasthenia gravis test QMG
Functional tests
6M-WT
Timed up and go (x 3)
Five times Sit-to-stand test
Time water swallow
Performance outcome measures
Exercise physiology testing
Systemic arterio-venous oxygen difference (calculated from measurement of cardiac output and rate of oxygen utilization during incremental exercise)
6MWT WITH CARDIORESPIRATORY
STANDARDIZED LACTATE PRE- POST-EXERCISE
Dynamometer
Biodex/ATLIS
30 SECOND SIT-TO-STAND
NINE HOLE PEG TEST
FUNCTIONAL MUSCLE TEST
6 MINUTES CHEWING TEST (PILOT)
GAITRITE
Activity meters (including sleep monitoring)
Spirometry
Patient-reported outcome measures Measurements of patient function or feeling
NMDAS/NPMDS Section IV
Quality of Life: PROMIS
Quality of Life: WHOQOL
Fatigue scale: CIS
Fatigue scale: FSS
Fatigue scale: MFI
PGIC
WHYMPI

PUBLISHED > 25

SUBMITTED 1

ONGOING 7

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

ORIGINAL COMMUNICATION

Redefining phenotypes associated with mitochondrial DN… 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 Ver… · Massimo Zeviani[16] · Gabriele Siciliano[1]

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

ORIGINAL COMMUNICATION

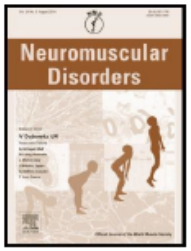
The m.3243A>G mitochondrial DNA mutation and related phenotypes. A matter of gender?

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

Accepted Manuscript

Title: "Mitochondrial neuropathies": a survey from the large cohort of the Italian Network

Author: Michelangelo Mancuso, Daniele Orsucci, Corrado Angelini, Enrico Bertini, Valerio Carelli, Giacomo Pietro Comi, Antonio Federico, Carlo Minetti, Maurizio Moggio, Tiziana Mongini, Paola Tonin, Antonio Toscano, Claudio Bruno, Elena Caldarazzo Ienco, Massimiliano Filosto, Costanza



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

ancuso[a,*], C. Angelini[b], E. Bertini[c], V. Carelli[d], G.P. Comi[m], C. Minetti[f],

RESEARCH ARTICLE

Myoclonus in Mitochondrial Disorders

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

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[2]Neurological Clinic, University of Padova, and (C.A.) IRCCS S. Camillo, Venice, Italy
[3]Bambino Gesù Children's Research Hospital, Rome, Italy
[4]IRCCS Istituto delle Scienze Neurologiche di Bologna, Bellaria Hospital, Bologna, Italy and
Department of Biomedical and Neuromotor Sciences (DIBINEM), University of Bologna, Bologna, Italy

Phenotypic heterogeneity of the 8344A>G mtDNA "MERRF" mutation

Michelangelo Mancuso, MD, PhD
Daniele Orsucci, MD
Corrado Angelini, MD, PhD
Enrico Bertini, MD, PhD

ABSTRACT

Objectives: Myoclonic epilepsy with ragged-red fibers (MERRF) is a rare mitochondrial syndrom… mostly caused by the 8344A>G mitochondrial DNA mutation. Most of the previous studies ha… been based on single case/family reports or series with few patients. The primary aim of this stu… was the characterization of a large cohort of patients with the 8344A>G mutation. The secon… ary aim was revision of the previously published data.

FONDAZIONE I.R.C.C.S.
ISTITUTO NEUROLOGICO CARLO BESTA

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Barbara Garavaglia
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Eleonora Lamantea
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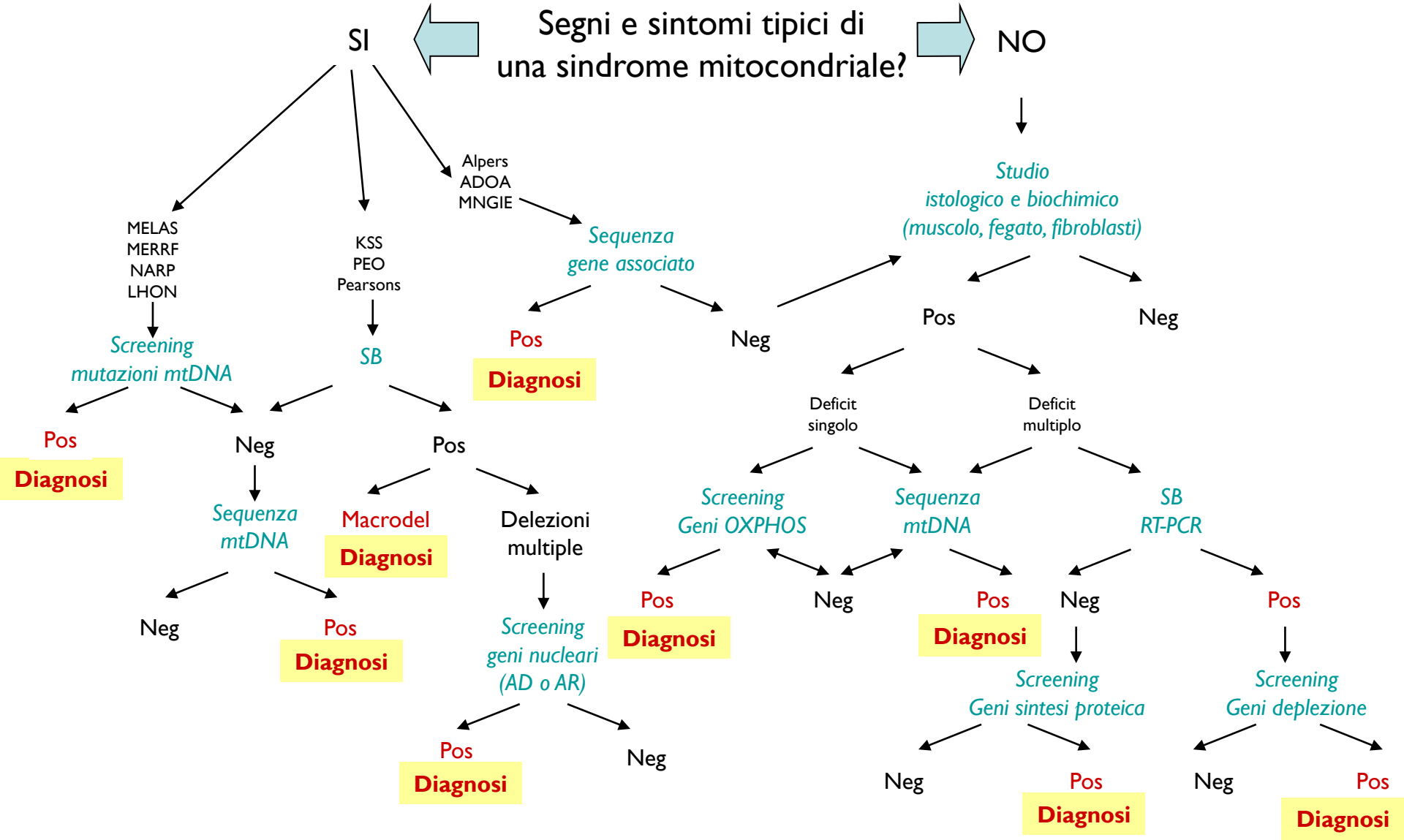
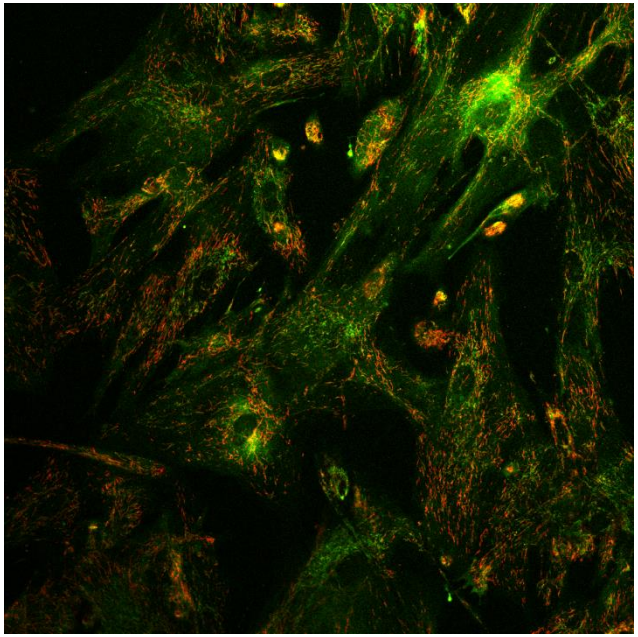
Mitocon ONLUS
Insieme per lo studio e la cura delle malattie mitocondriali

TeleThon

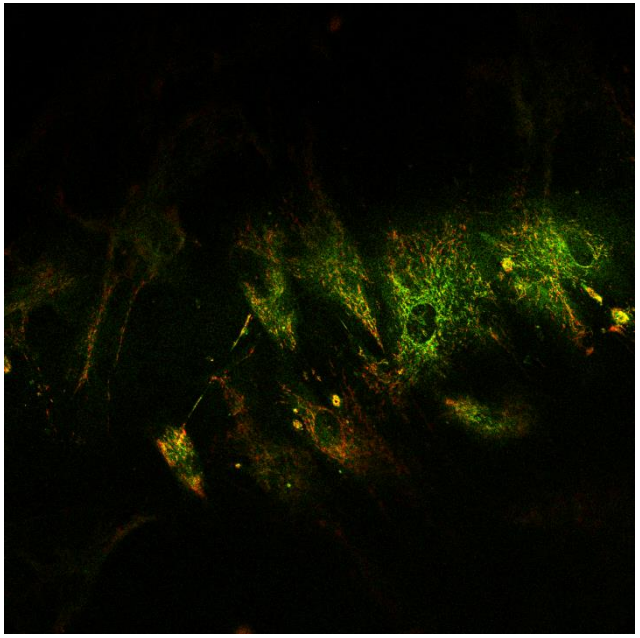


E se non si raggiunge una diagnosi?

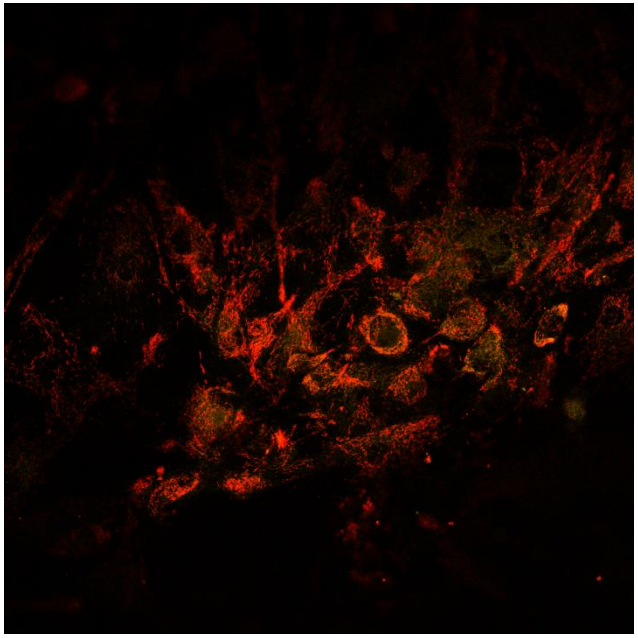
Mb pz 1



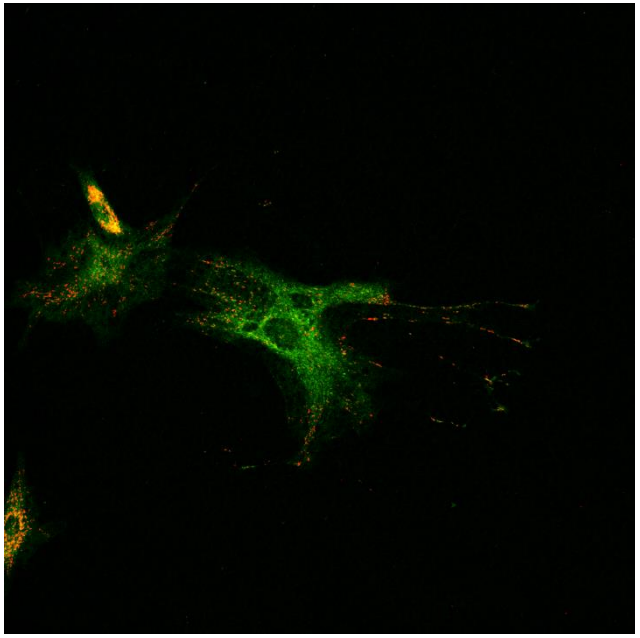
Mb pz 3



Mb ctrl



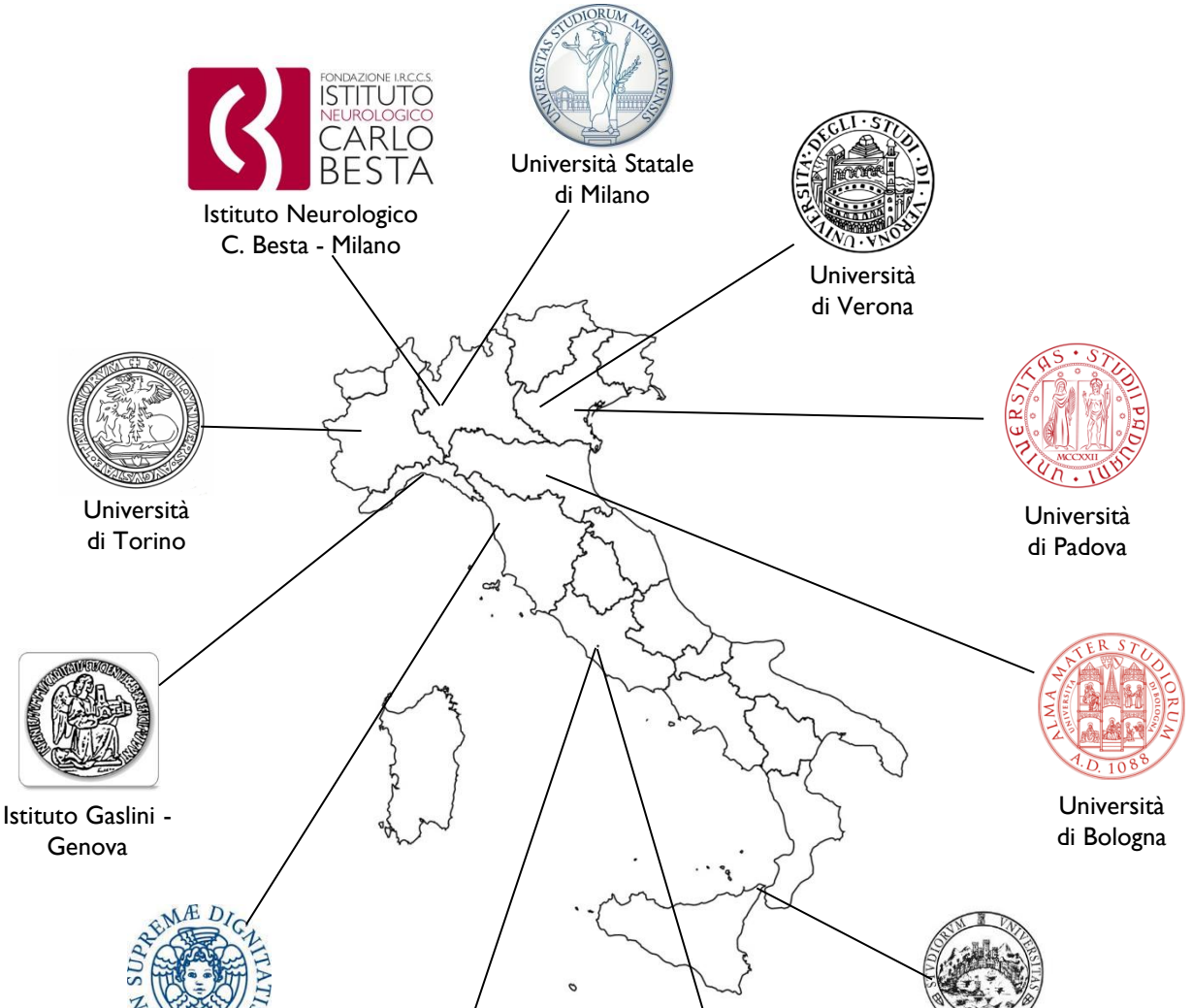
Mb ctrl + valinomycin

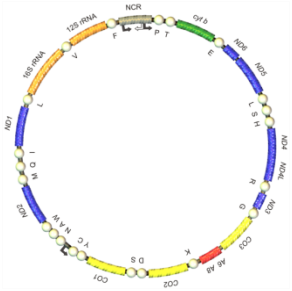


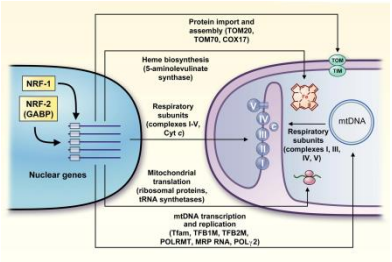
Pz 1 = Ragone

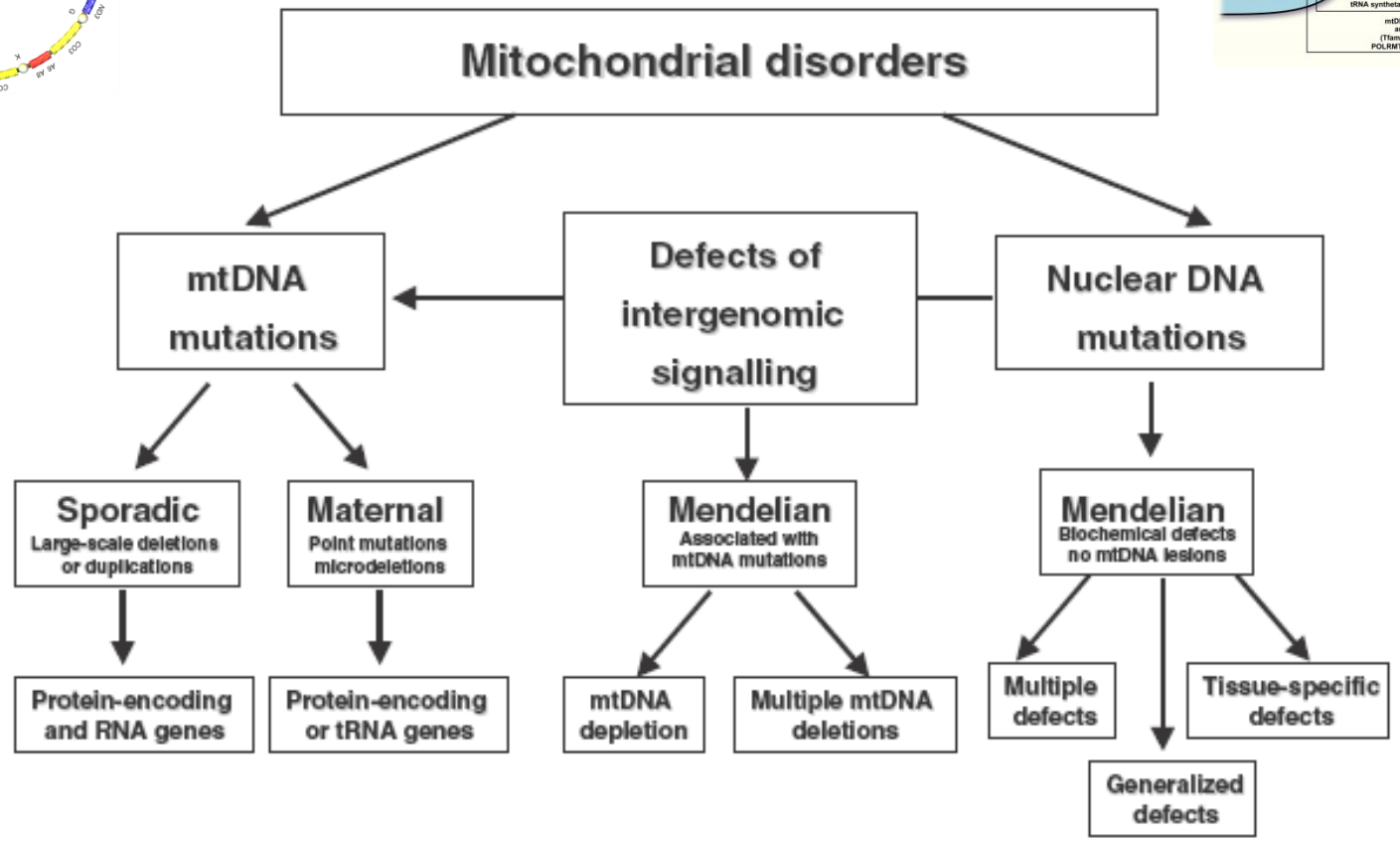
Pz 3 = Marini

Il Network Italiano per le Malattie Mitocondriali

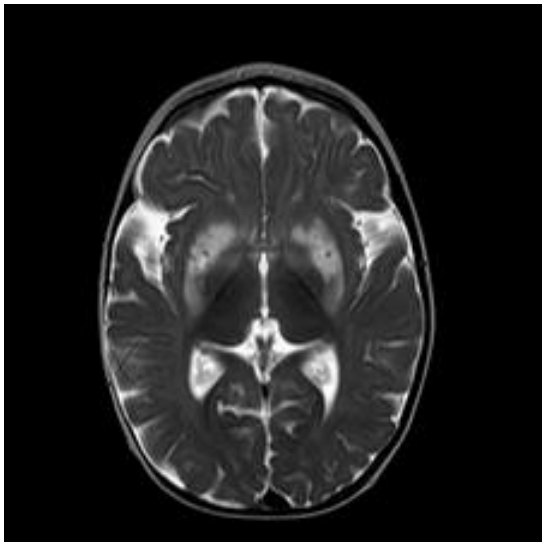


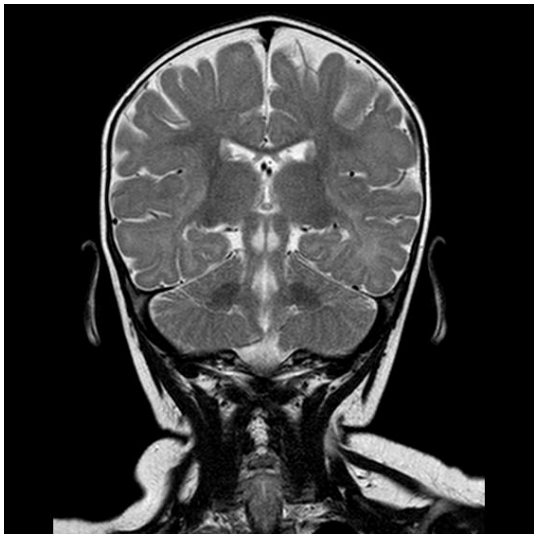


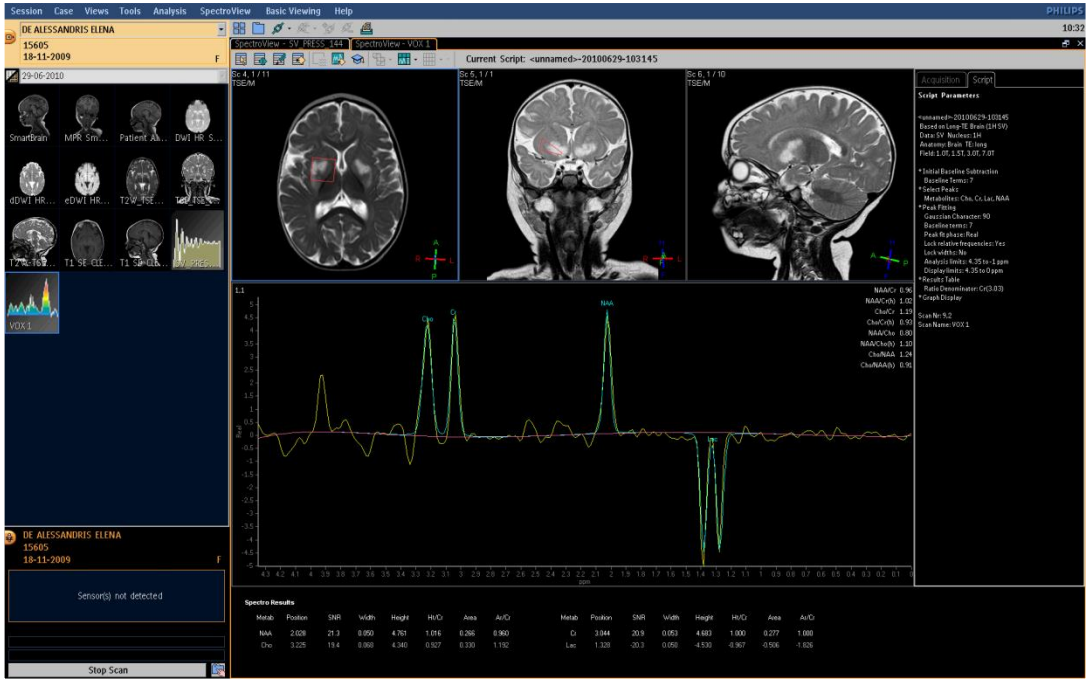




Le malattie mitocondriali possono essere sporadiche, trasmesse per via matrilineare o come carattere autosomico (recessiva, dominanate o X-linked).



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15605
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10:32
SpectroView - SV_PRESS_144
SpectroView - VOX 1
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TSE/M
Sc 5, 1 / 1
TSE/M
Sc 6, 1 / 10
TSE/M
Acquisition
Script
Script Parameters
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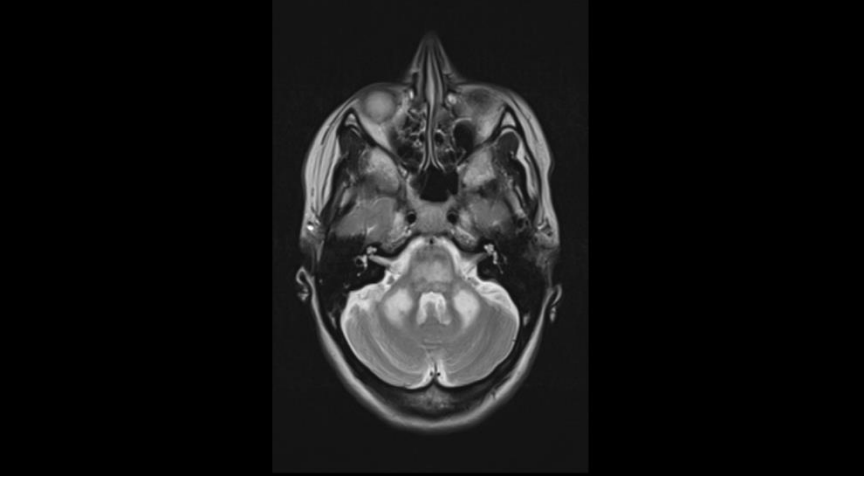
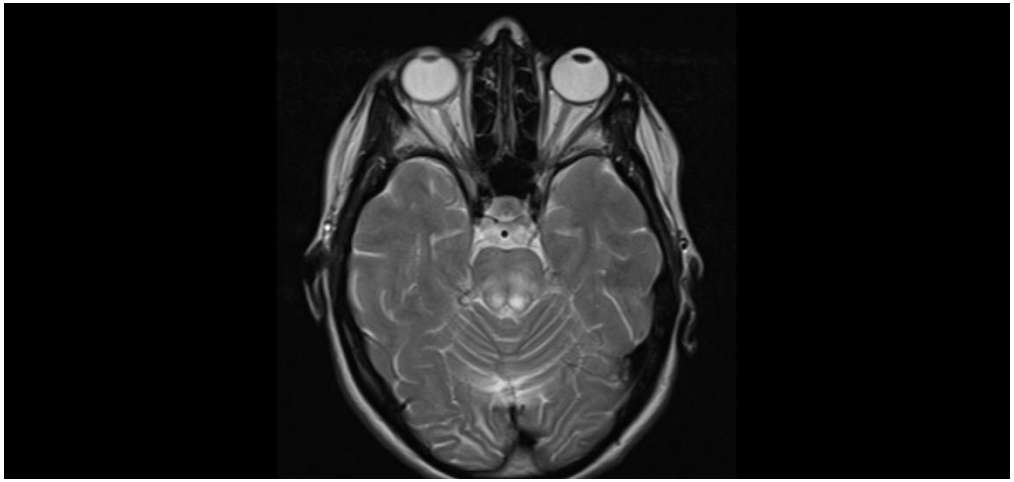
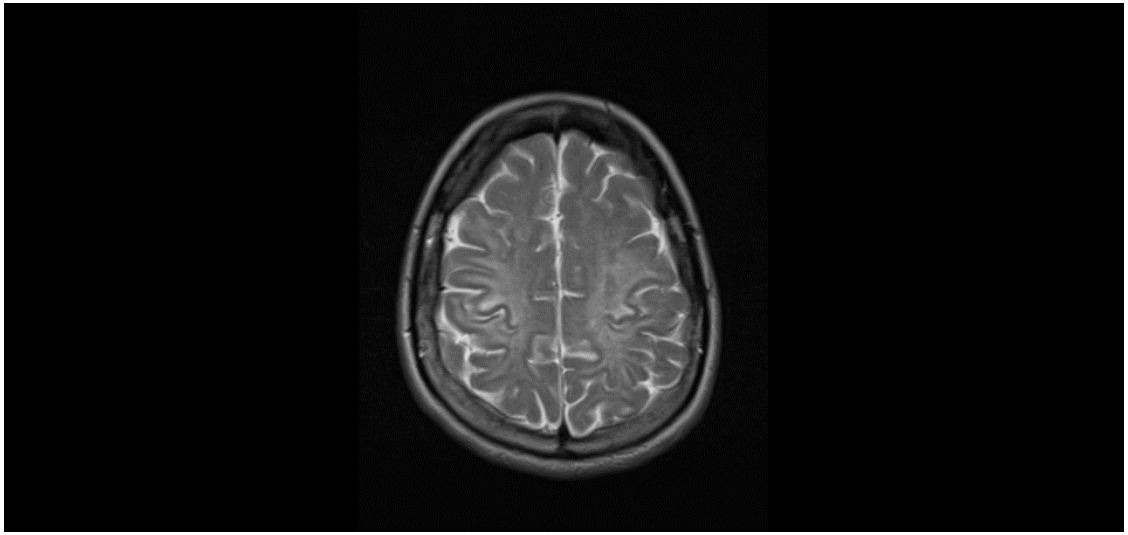
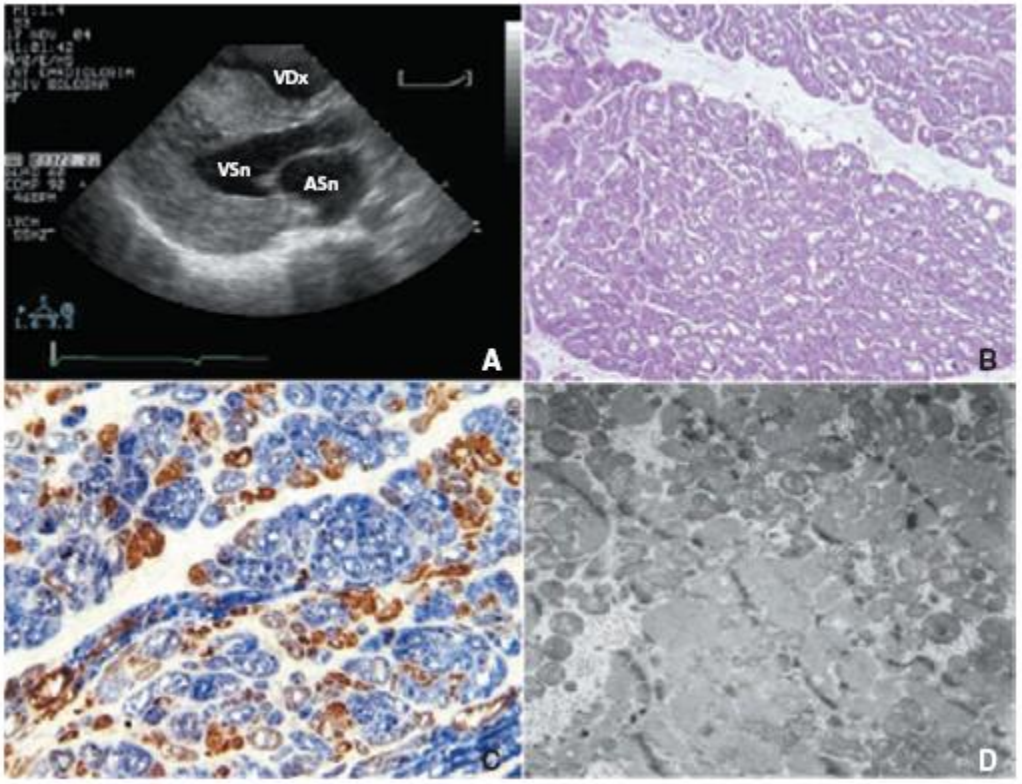
Based on Loop-TE Brain (1H SV)
Data: SV Nucleus: 1H
Anatomy: Brain TE: long
Field: 1.0T, 1.5T, 3.0T, 7.0T
Initial Baseline Subtraction
Baseline Terms: 7
Select Peaks
Metabolites: Cho, Cr, Lac, NAA
Peak Fitting
Gaussian Character: 90
Baseline terms: 7
Peak fit phase: Real
Lock relative frequencies: Yes
Lock widths: No
Analysis limits: 4.35 to -1 ppm
Display limits: 4.35 to 0 ppm
Results Table
Ratio Denominator: Cr(3.03)
Graph Display
Scan Nr: 52
Scan Name: VOX 1
NAA/Cr 0.96
NAA/Cr(h) 1.02
Cho/Cr 1.19
Cho/Cr(h) 0.93
NAA/Cho 0.80
NAA/Cho(h) 1.10
Cho/NAA 1.24
Cho/NAA(h) 0.91
NAA
Cho
Cr
Lac
ppm
Spectro Results
Metab Position SNR Width Height Ht/Cr Area Ar/Cr
NAA 2.028 21.3 0.050 4.761 1.016 0.266 0.960
Cho 3.225 19.4 0.068 4.340 0.927 0.330 1.192
Cr 3.044 20.9 0.053 4.683 1.000 0.277 1.000
Lac 1.328 -20.3 0.058 -4.530 -0.967 -0.506 -1.826
29-06-2010
SmartBrain
MPR Sm...
Patient An...
DWI HR S...
dDWI HR...
eDWI HR...
T2 W_TSE...
T2 W_TSE_SP...
T2 W_TSE...
T1 SE CLE...
T1 SE CLE...
SV_PRES...
VOX 1
DE ALESSANDRIS ELENA
15605
18-11-2009
F
Sensor(s) not detected
Stop Scan



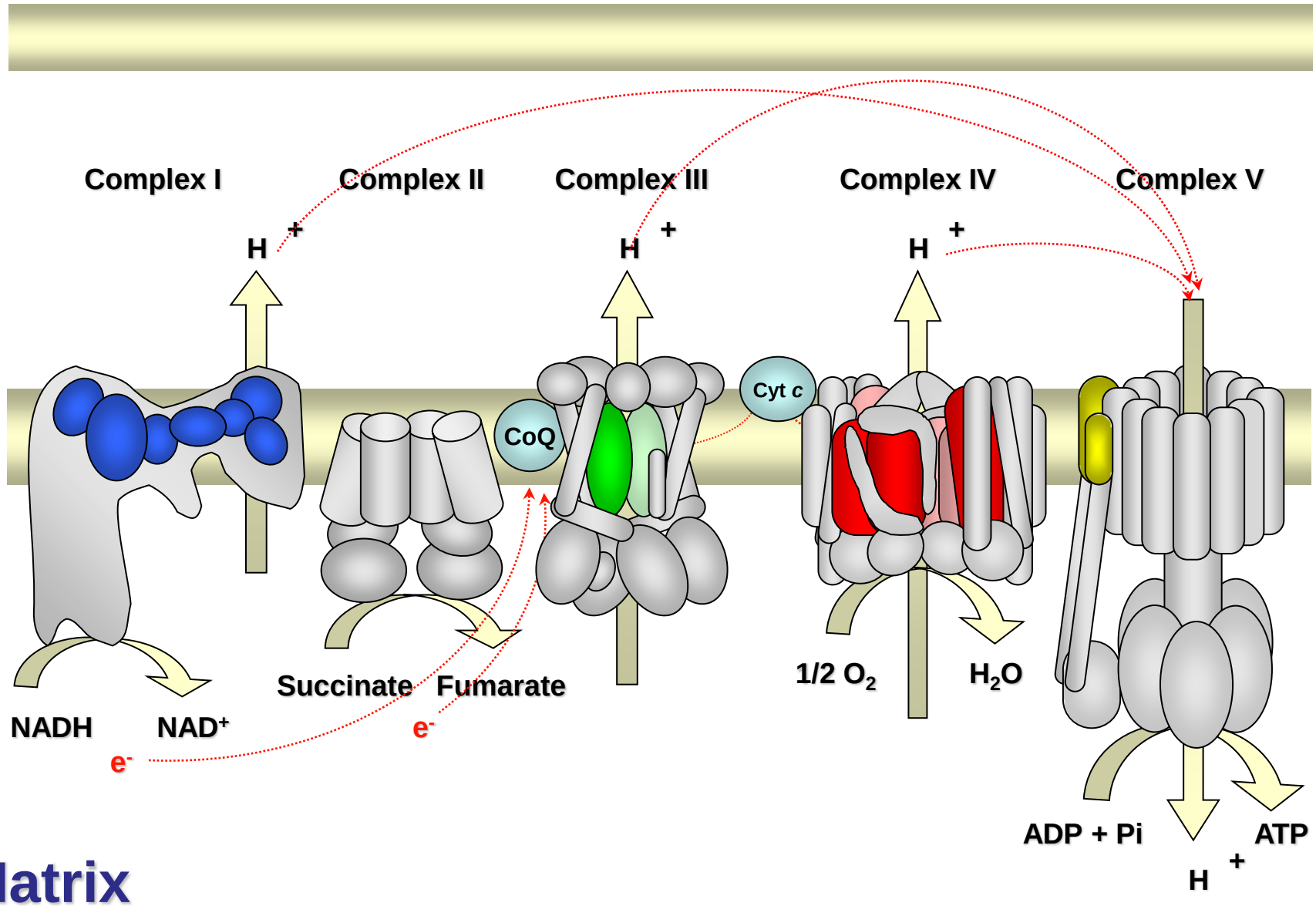




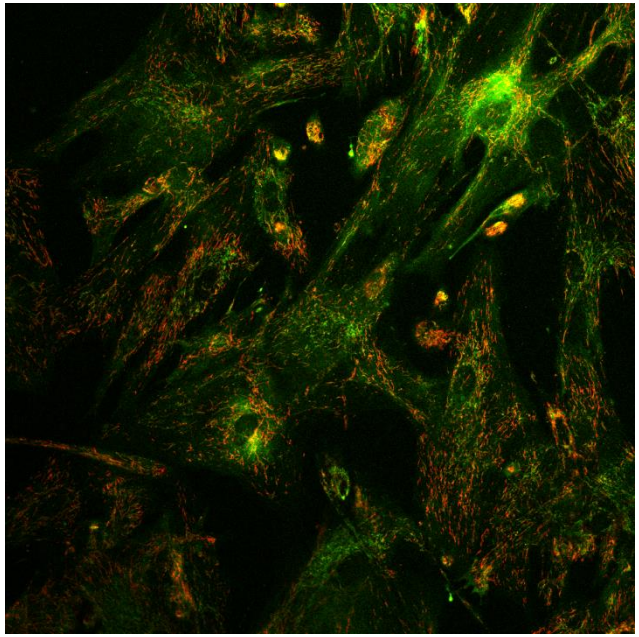
VALUTAZIONE CARDIOLOGICA



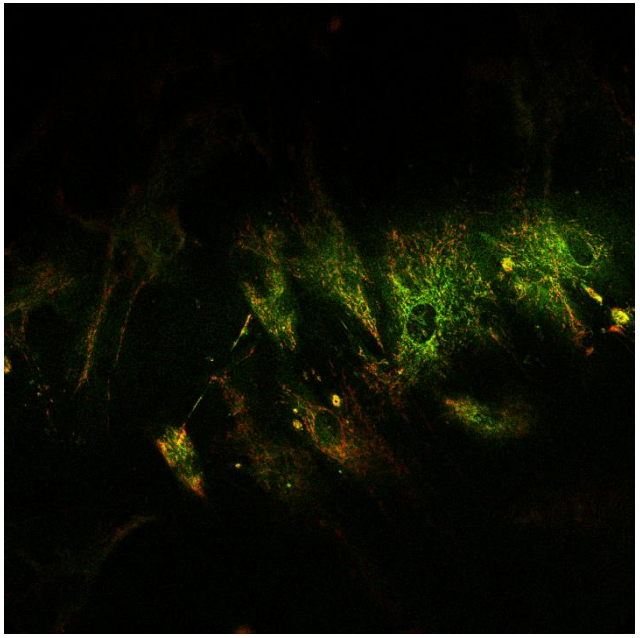
Cardiopatia dilatativa
Cardiopatia ipetrofica
Disturbi del ritmo


Cytoplasm
Complex I
Complex II
Complex III
Complex IV
Complex V
H +
H +
H +
CoQ
Cyt c
NADH
NAD+
e-
Succinate
Fumarate
e-
1/2 O2
H2O
ADP + Pi
ATP
H +
Matrix

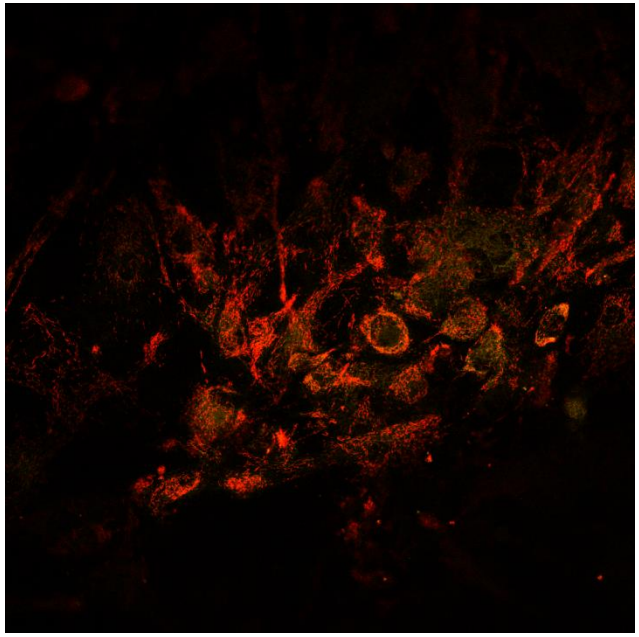
Mb pz 1



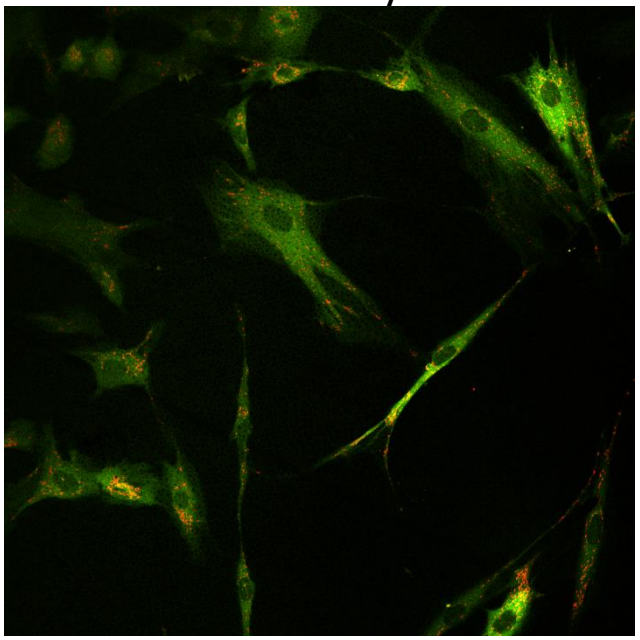
Mb pz 3



Mb ctrl



Mb + valinomycin



Pz 1 = Ragone

Pz 3 = Marini