Mitocondri e neurologia di genere

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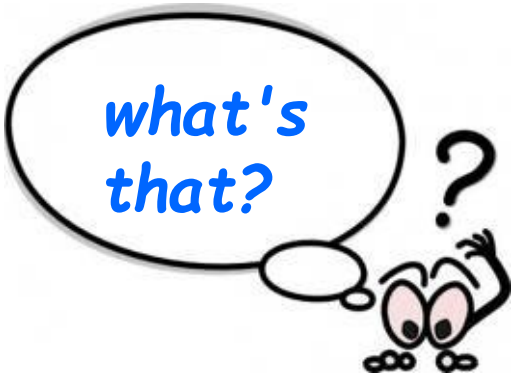
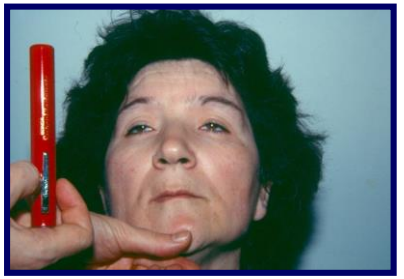
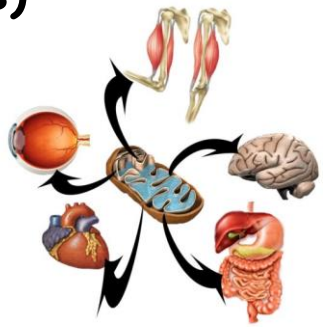
Mitochondrial diseases

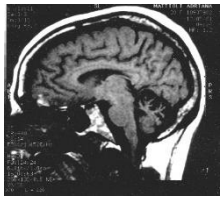


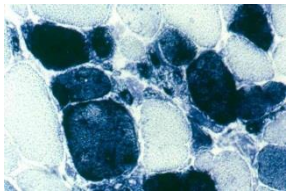
Complicated disorders with myriad signs and symptoms and body systems involved (all tissues may be affected except red blood cells)

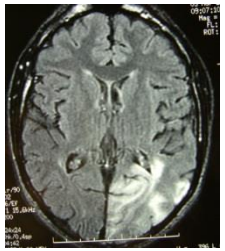


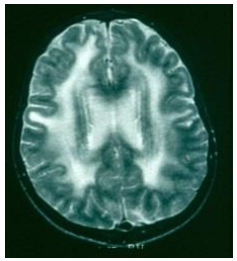
- significant clinical and genetic heterogeneity
- syndromic and non-syndromic
- often multi-system diseases
- onset between birth and senescence
- a common cause of chronic morbidity, more prevalent than previously thought



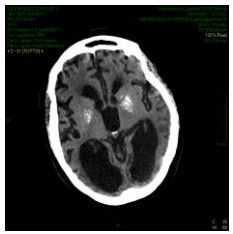


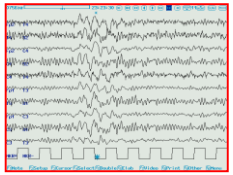


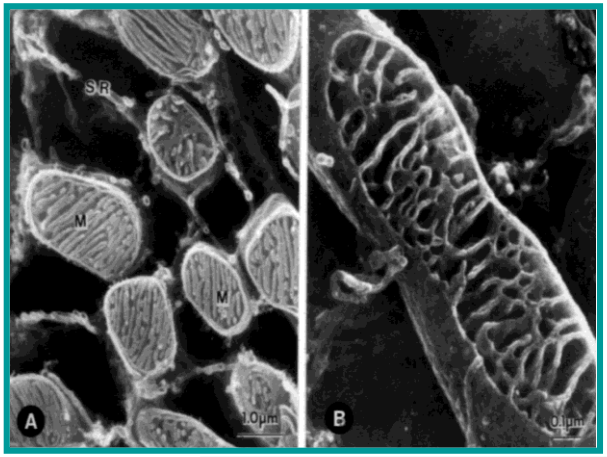


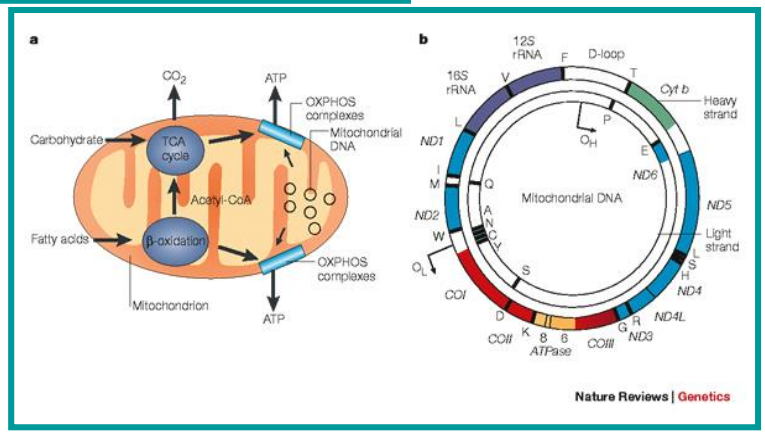


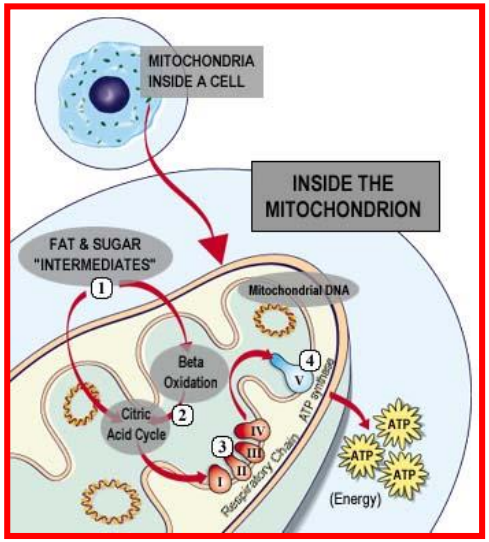
- ➢ increasing evidence that mitochondrial dysfunction plays an important role in the pathogenesis of many neurodegenerative disorders









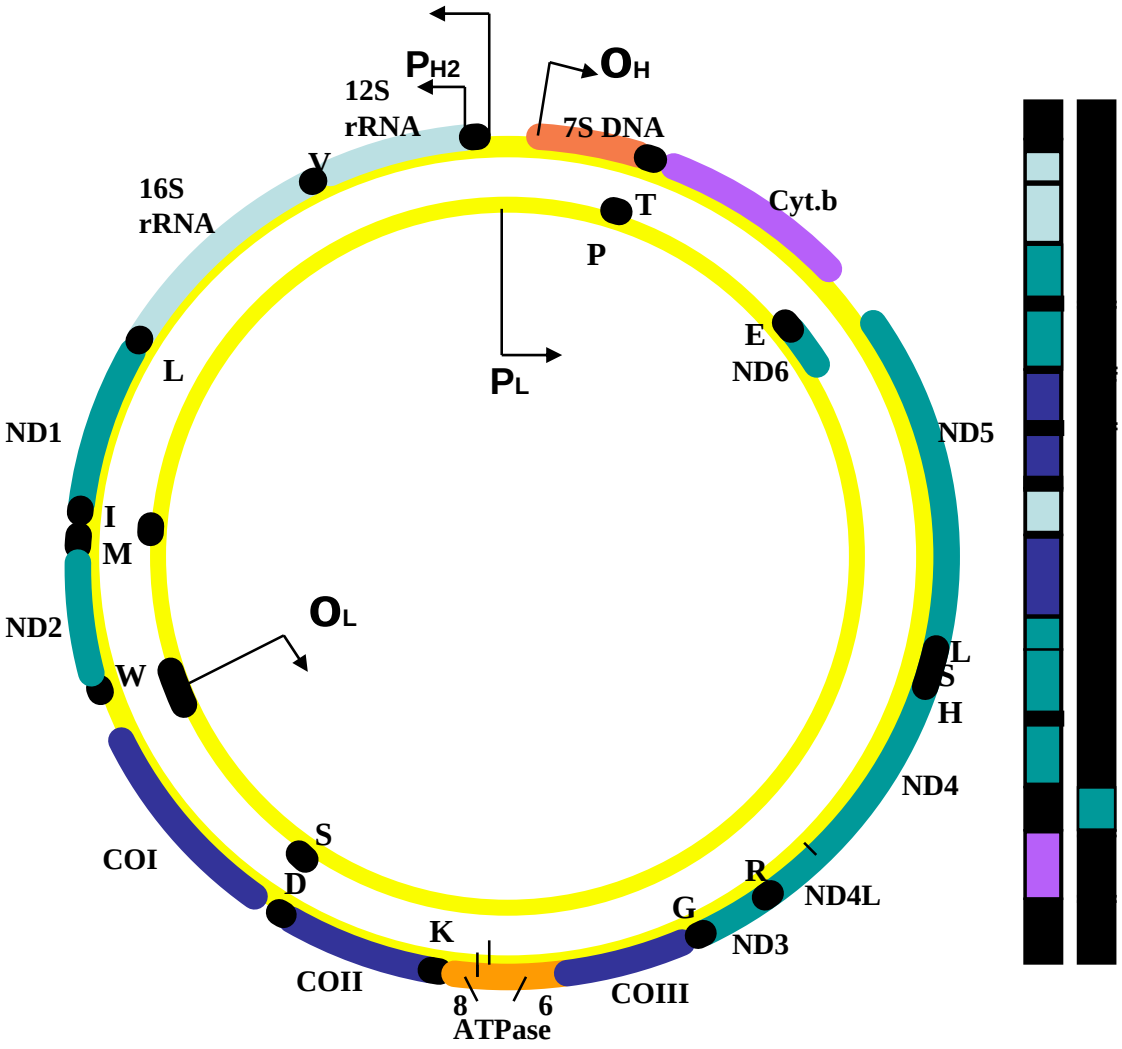


Mitocondria are found in all nucleated cells and are the principal generators of cellular ATP by oxidative phosporylation.

Mitochondrial DNA is a fossil molecule proving that endosymbiosis did occur, when, about 1.5 billion years ago, probacteria populated primordial eukariotic cells.

Unlike fossil, mtDNA has lost its indipendence, but keeps functioning under the overarching control of the nuclear genome.

DNAmt



·Double-stranded circle of 16569 bp containing 37 genes: 13 proteins (subunits of complex I, III, IV and V of respiratory chain), 2rRNAs, 22 tRNAs

·Its genetic code differs from that of nDNA

·It is tightly packed with information, because it contains no introns

·It is in proximity to the inner membrane, site of free radicals formation, and lacks of histone coverage

·It has less efficient repair mechanisms than nDNA

·It is subject to spontaneous mutations at a higher rate than nDNA

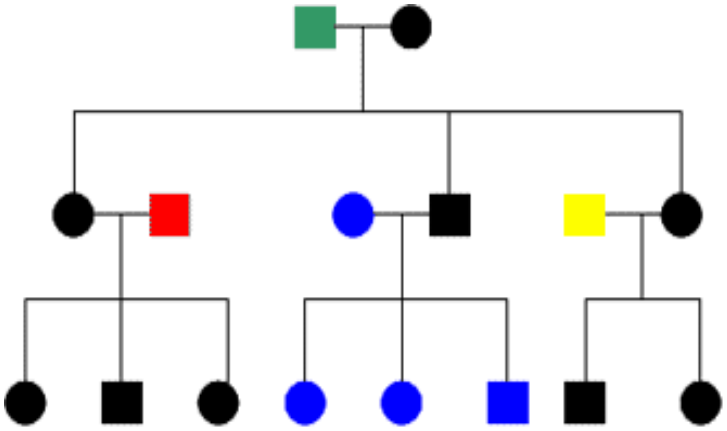
·It is present in hundreds or thousands of copies in each cell (2 to 10 genomes per mitochondrion)

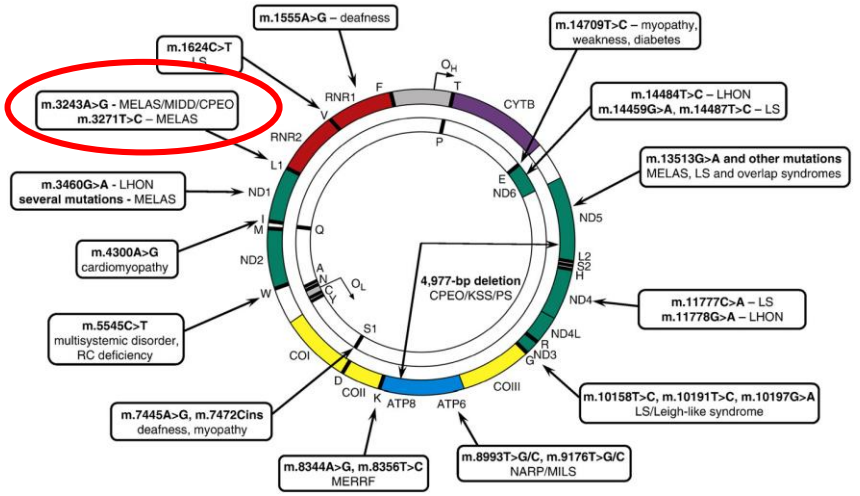
·It is transmitted by maternal inheritance

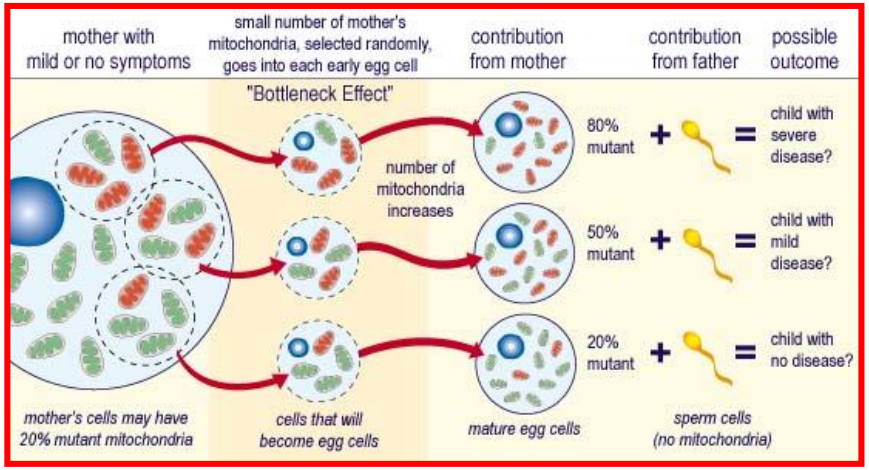
mtDNA

- maternal transmission
- heteroplasmy
- mitotic segregation
- threshold effect

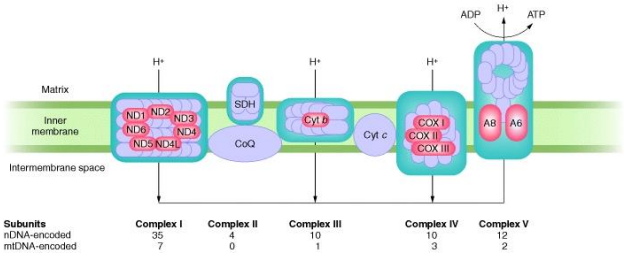
clinical heterogeneity





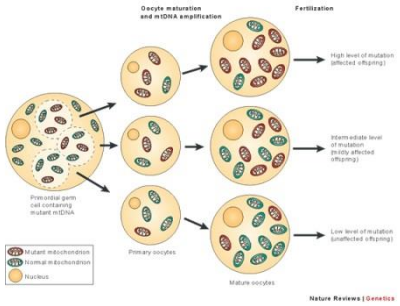


primary mitochondrial disorders -> respiratory chain defects genetic heterogeneity

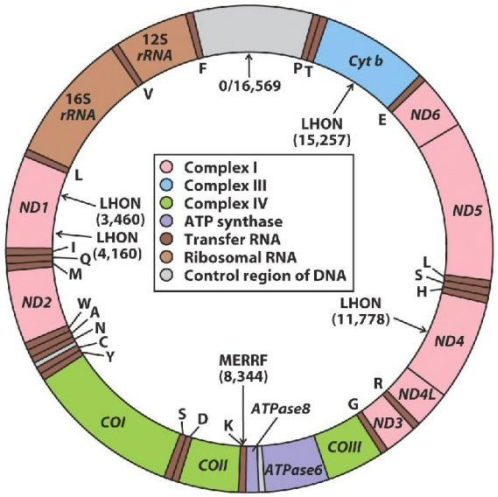


dual genomic contribution in the assembly of mitochondrial respiratory complexes

> 1500 mitocondrial proteins; only 13 encoded by mtDNA



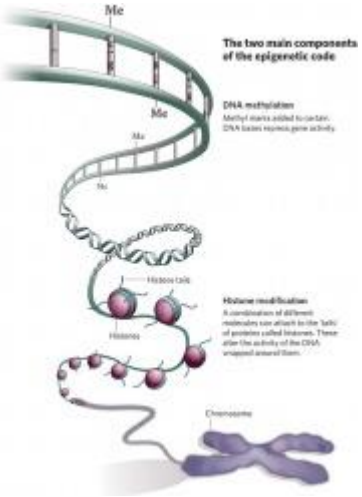
- maternal inheritance
- heteroplasmy
- mitotic segregation
- threshold effect



- mtDNA single deletion
- mtDNApoint mutations

cross-talk

- mtDNA multiple deletion
- mtDNA depletion



normal mtDNA

mendelian

Mitochondrial diseases

- Best known phenotypes in adulthood

PEO Progressive External Ophthalmoplegia

KSS Kearns Sayre Syndrome

MERRF Myoclonic Epilepsy with Ragged Red Fibers

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

LHON (Leber Hereditary Optic Neuropathy)

- ❖ In adults: minimum prevalence rate for mtDNA mutations 1:5000; for nuclear mutations 2.9: 100.000 (Gorman et al. 2015)
- Most common mtDNA mutation: the A3243G represents the most common mtDNA mutation with an estimated frequency of about 16.3/100.000 (Majamaa et al. 1998)
- Most common nuclear gene involved: polymerase-gamma 1 POLG1

single
mtDNA
deletion
sporadic

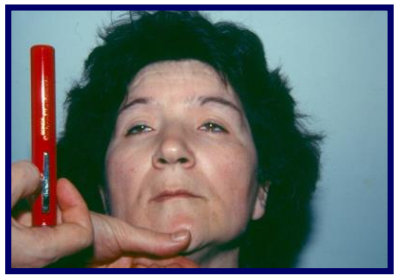
S-Del, PointMut, M-Del
sporadic, maternal, dominant
recessive

single
mtDNA
deletion
sporadic

PEO → PEO plus → KSS

mild
myopa
thy

slowly
progres
sive



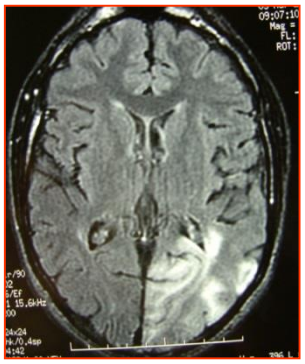
myopathy
> = <
CNS

variably
multisy
stem

variable
severity
and
progression

CNS
>>>>
myo
pathy

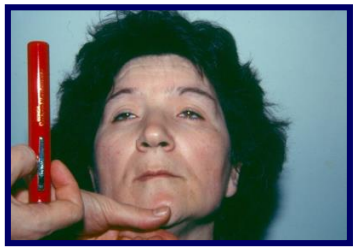
severe



➢mutation A3243G - phenotypes
most common mutation of mtDNA

PEO

myopa
thy
>>>>
CNS



diabetes/neurosensorial deafness

mild

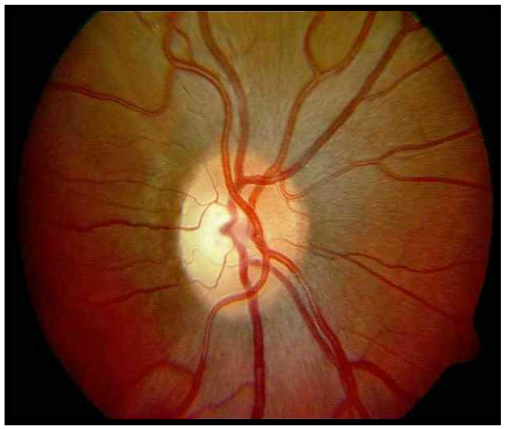
myopa
thy
>>>>
CNS

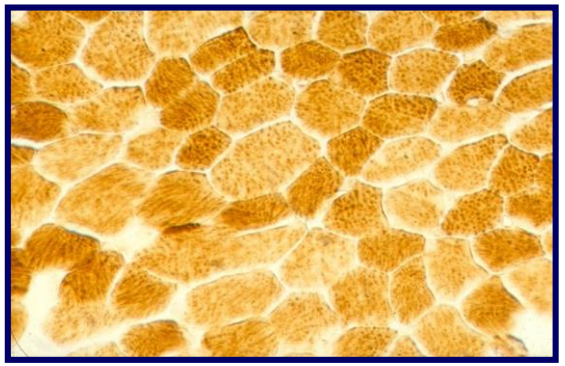
MELAS

CNS
>>>>
myo
pathy

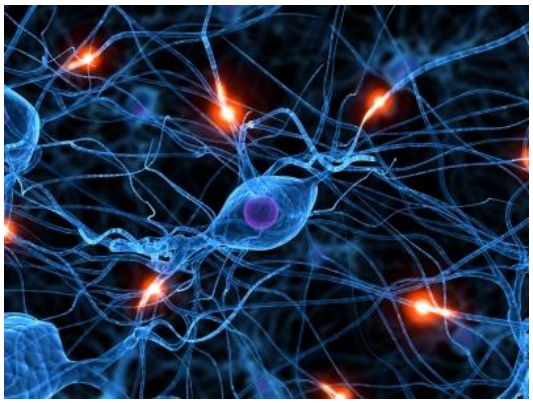
cardiomyopaty

- Leber's hereditary optic neuropathy (LHON)
  - 3 "primary", several "secondary" mutations in ND genes
  - maternally inherited cause of blindness in young men
  - multisystemic, although optic nerve selectively affected
  - muscle bx: no RRF
  - mutations are homoplasmic





Mitochondria and neurodegeneration

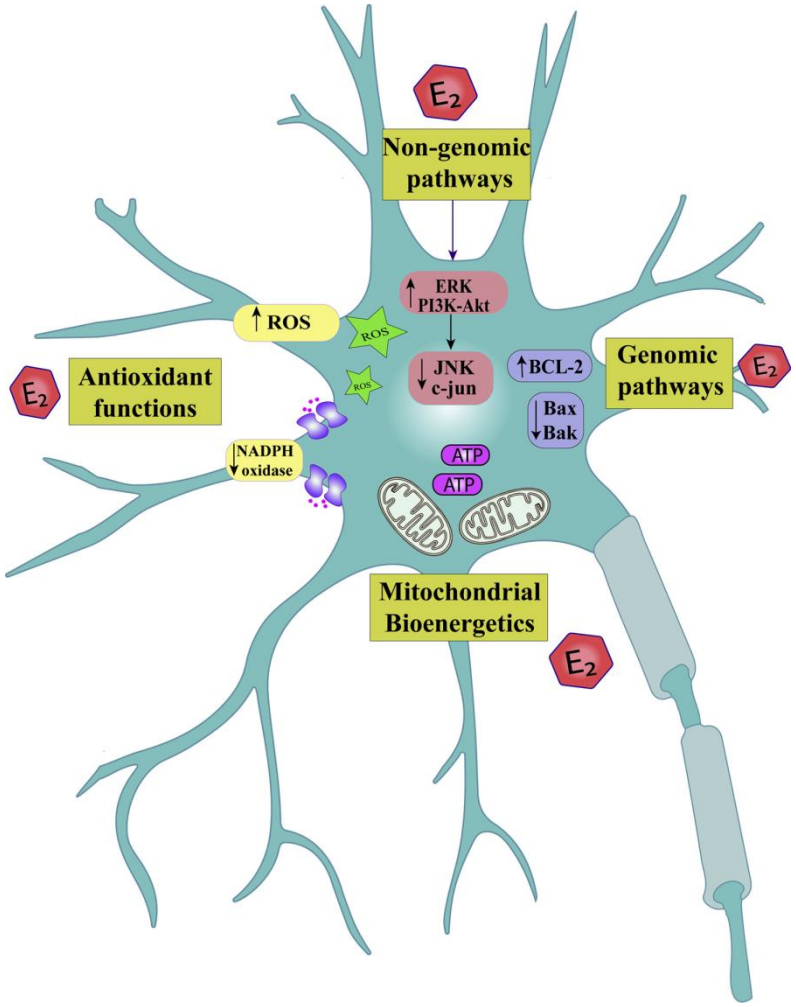


- Mitochondria play a pivotal role regulating survival and death of neurons, and mitochondrial dysfunction has been shown to contribute to neuronal death seen in neurodegenerative diseases.
- Mitochondria are in charge of energy production and regulate oxidative stress; are the major source of ATP playing a central part in modulation of neuronal excitability and synaptic transmission
- Mitochondria are the site of the first steps of steroidogenesis and the target of sex steroids

➢ It has been shown that both estrogens and androgens possess multiple effects on mitochondria that promote or preserve mitochondrial function during excitotoxicity and oxidative stress.

Mitochondria and neurodegeneration

- As the nervous system has a high metabolic rate and a low capacity of energy storage, dysfunction of brain mitochondria has devastating consequences
- Brain mitochondrial functions decline with age and it's has been demonstrated that sex steroid loss is involved in the dysregulation of mitochondrial functions
- Chronic diseases with bioenergetic defects that implicate mitochondrial dysfunction include Alzheimer's disease and Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, Freidreich's ataxia
- Males predominantly utilize proteins while females predominantly use lipids as a fuel source within mitochondria -> these differences may significantly affect cellular survival
- Sex differences in brain mitochondrial functions may explain, at least partially, the influence of sex steroids on neurodegenerative diseases such as AD and PD.



Mohajeri et al. 2019

estrogens protects neurons against neurodegeneration via stabilizing mitochondrial function by four mechanisms

- nuclear transcriptional effects
- mitochondrial transcriptional effects
- rapid, short-term non-genomic signalling
- direct antioxidant effects

Mitochondria and neurodegenerative disorders

- Mitochondrial dysfunction has long been observed in Parkinson and animal models and recent studies have revealed that genes associated with autosomal recessive forms of PD such as PINK1 and Parkin are directly involved in regulating mitochondrial morphology and maintenance, and in mitochondrial degradation (mitophagy)
- Some cases of AD and PD can be interpreted as affecting mitochondrial function, quality control, and mtDNA integrity.
- MtDNA lineages and haplogroups, are important risk factors for AD and PD.
- Somatic mtDNA mutations are elevated in AD, PD, both in brains and also systemically.

- Mitochondrial dysfunction may in part provide a unifying genetic and pathophysiology explanation for some aspects of AD, PD, and other neurodegenerative diseases.

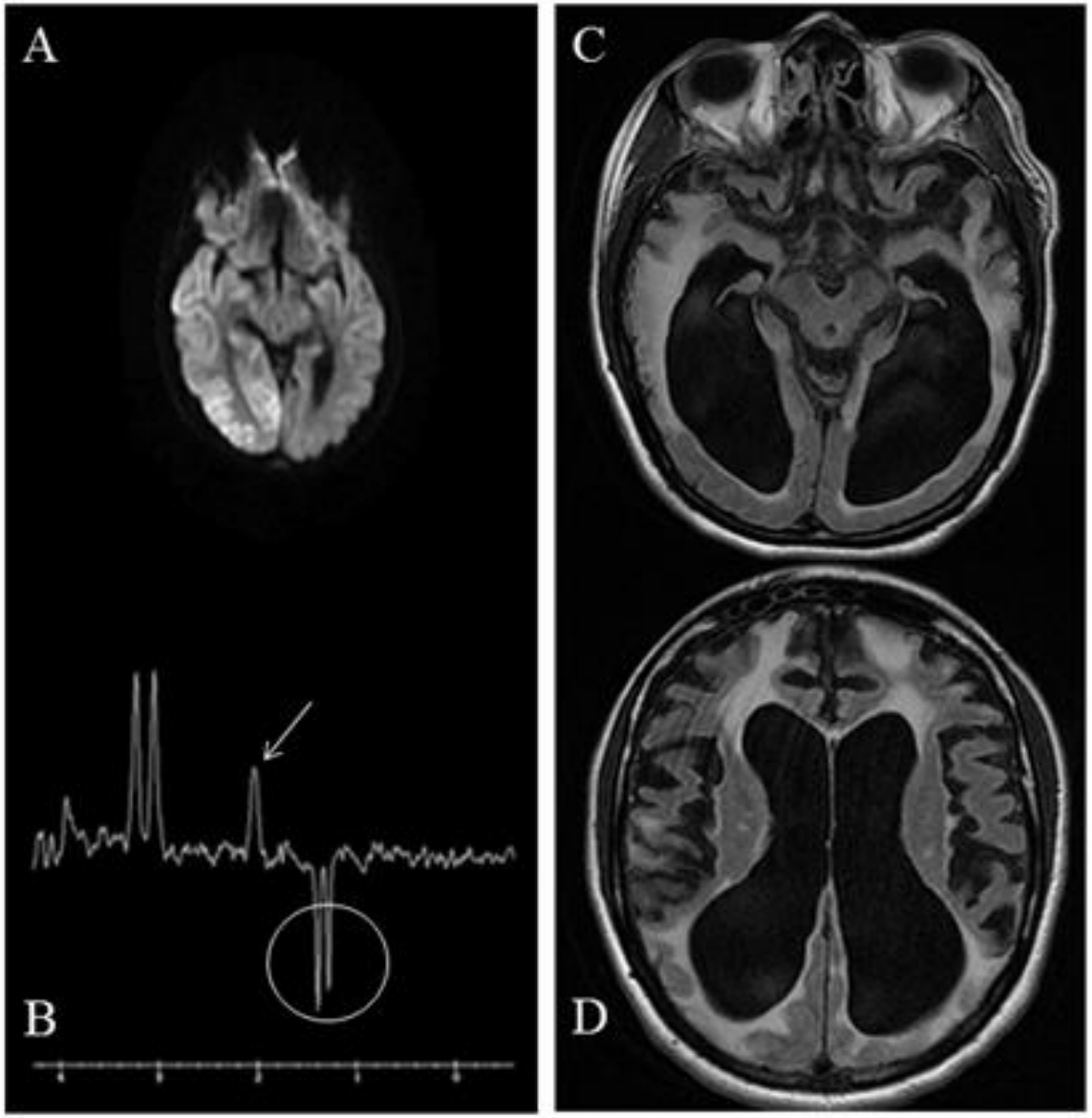
Mitochondria and neurodegeneration

- Alzheimer's disease: retrospective epidemiological studies in post-menopausal women indicate that estrogen replacement therapy is associated with a reduction in the risk and progression and several studies reported an increased risk of AD with early menopause
- However. probably because AD is highly multifactorial, epidemiological data failed to clearly support the hypothesis of sex steroid hormones influence
- On the other hand, animal models support an important influence of ovarian steroids on the evolution of mitochondrial AD-induced disorders
- Recent findings highlight that, in addition to sex differences in mitochondrial function, the effects of sex steroids on mitochondria could differ between men and women
- Mitochondrial energetic metabolism and oxidative stress regulation are involved in AD sex bias

Mitochondrial diseases and cognitive functions

- Dementia has been reported in MELAS, MERRF, CPEO, KSS, MNGIE, NARP, Leigh syndrome, and POLG1-phenotypes
- Mild cognitive impairment in our patients shows a consistent pattern, independently from phenotype, characterized by deficit of mental control, short term memory and visual selective attention
- Cognitive functions and intellectual abilities may decline from initially focal cognitive impairment to lastly dementia
- Morphological abnormalities do not always correlate with clinical manifestations and include focal or diffuse atrophy, focal or diffuse cortical, subcortical, or white matter lesions, cystic lesions, lacunas or calcifications. Dementia in MELAS do not correlate with SLEs

➢ No specific clinical-morphological patterns



MELAS

severe, diffuse brain atrophy and dementia

J Neurol (2014) 261:504–510
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

In the series of patients enrolled in the Italian Registry of Mitochondrial patients, among the 133 patients harbouring the m.A3243G variant, there is statistically significant difference in men (P = 0.019) in the "MELAS" group (64,7%) vs "non-MELAS" group (42.7 %)

- Male gender seems to represent a risk factor for the development of stroke-like episodes

Pickett et al. 2018 found for two phenotypes, the effect of sex significant (ptosis and myopathy). Moreover, more males (17.9%) were affected by stroke-like episodes than females (10.4%), although this did not reach significance

Mitochondrial diseases migraine

Migraine or migraine-like headaches are a prominent feature of specific mitochondrial phenotypes or genotypes. Headache can be sometimes the only clinical feature in oligosymptomatic maternal relatives of patients mtDNA mutations (mostly m.3243A>G)

Original Article

Cephalalgia
International Headache Society

Cephalalgia
2018, Vol. 38(6) 1093–1106

DOI: 10.1177/0333102417723568
journals.sagepub.com/home/cep
SAGE

Migraine in mitochondrial disorders: Prevalence and characteristics

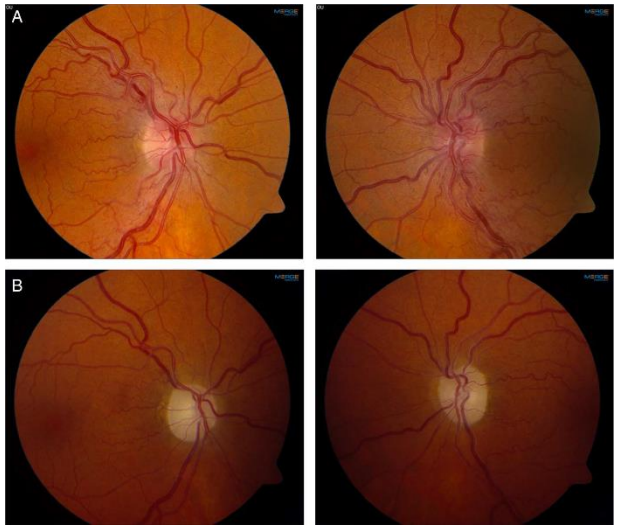
Catello Vollono[1,*], Guido Primiano[1,*], Giacomo Della Marca[1], Anna Losurdo[2] and Serenella Servidei[1]

In our cohort of 93 mitochondrial patients (age 16-78), migraine is present in 35.5%, with a much higher prevalence compared to general population, independently from gender (some frequency in males and females), genotype or phenotype.

When the patients are divided by sex the prevalence in men is 38.7%, much higher than in all studies from the literature (about 6%) and very different from the typical ratio of 3:1 in favor of women in the general adult population

- ❖ Migraine without aura is the most common headache (84.8%).
- ❖ Mitochondrial patients with migraine show (vs non migraine)
- ✓ younger age
- ✓ significantly increased prevalence of epilepsy, myoclonus, sroke-like episodes Migraine is an early manifestation of the MDs characterized by prevalent CNS involvement
- ➢ Migraine in MDs is a common expression of vulnerability of the CNS to defects of the mitochondrial respiratory chain.

LHON



- Higher prevalence in males
- Due to mtDNA point mutations in complex I
- Characterized by the selective degeneration of retinal ganglion cells, leading to optic atrophy and loss of central vision
- Significant sex bias in the LHON pedigrees -> male offspring present with more severe visual loss and higher penetrance, and female offspring exhibit mild symptoms and low penetrance
- Clinical penetrance (incidence and prevalence) with 21–71% of men and 8–26% of women developing vision loss in their lifetime
- No definite genetic modifiers
- Metabolic basis for the unexplained male prevalence -> role of estrogens

doi:10.1093/brain/awq276 Brain 2011: 134; 220–234 | 220

BRAIN
A JOURNAL OF NEUROLOGY

Oestrogens ameliorate mitochondrial dysfunction in Leber's hereditary optic neuropathy

Carla Giordano,[1,*] Monica Montopoli,[2,*] Elena Perli,[1] Maurizia Orlandi,[1] Marianna Fantin,[3] Fred N. Ross-Cisneros,[4] Laura Caparrotta,[2] Andrea Martinuzzi,[3] Eugenio Ragazzi,[2] Anna Ghelli,[5] Alfredo A. Sadun,[4] Giulia d'Amati[1] and Valerio Carelli[6]

- Oestrogen receptor beta is localized to the mitochondrial network of human retinal ganglion cells with the unmyelinated portion of their axons in the retinal nerve fiber layer
- Multilayer cytoprotective effects induced by estrogens -> reduce the production of reactive oxygen species, restore membrane potential, limit apoptotic cell death, activate mitochondrial biogenesis, and improve energetic metabolism in LHON cybrids
- Oestrogen receptor mediated effects.

Conclusion

- Mitochondrial metabolic dysfunction is a common feature of neurodegeneration.
- It is becoming increasingly evident that mitochondrial metabolism and mitochondrial function are sexually dysmorphic.
- Mitochondrial energetic metabolism and oxidative stress regulation are likely involved in AD sex bias
- Male gender seems to represent a risk factor for specific clinical manifestation of mitochondrial disorders, such as Stroke-like episodes in MELAS and visual loss in LHON

Further studies of sexually dimorphic mitochondrial metabolism, cell signaling and pathophysiology may help in the generation of novel efficacious neuroprotective treatment strategies


GRAZAS
DANKIE
QUJAN
THANK YOU
TODA
ASANTE
TAKK
MITELA
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