Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Guido Primiano

La richiesta di competenza neurologica nel prossimo futuro

Sesta edizione

MITOCONDRIALI - Up to date

Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma

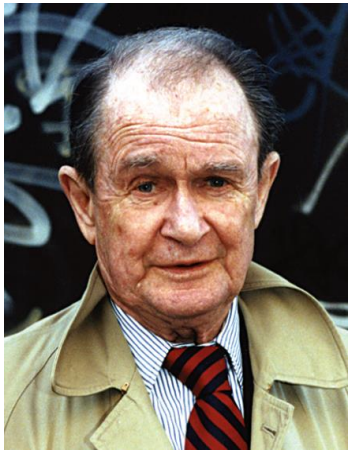
Dipartimento Universitario di Neuroscienze, UCSC, Roma

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

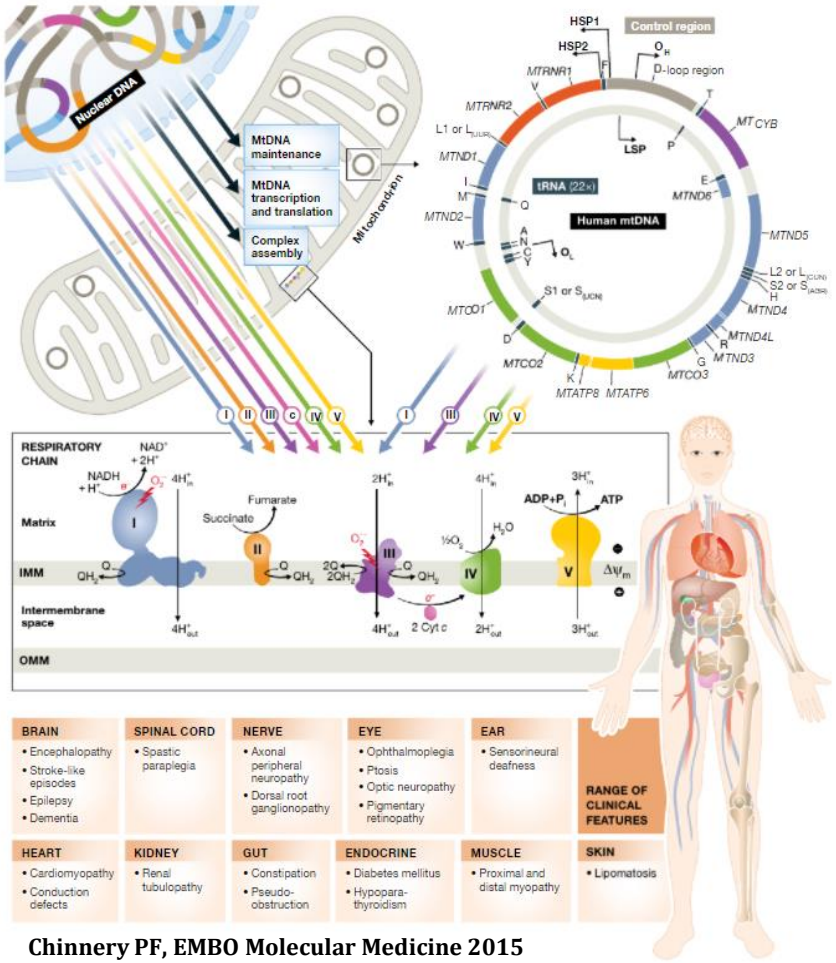
Mitochondrial Medicine

"In 1959, the first biochemical studies of a cell organelle in humans were undertaken, following observations made at the bedside of a patient with striking symptoms, never before encountered. These clinical observations, first, led to an idea about the origin of the symptoms and, second, to studies of the particular organelle: the **mitochondrion**"

Luft R. The development of mitochondrial medicine. PNAS 1994.



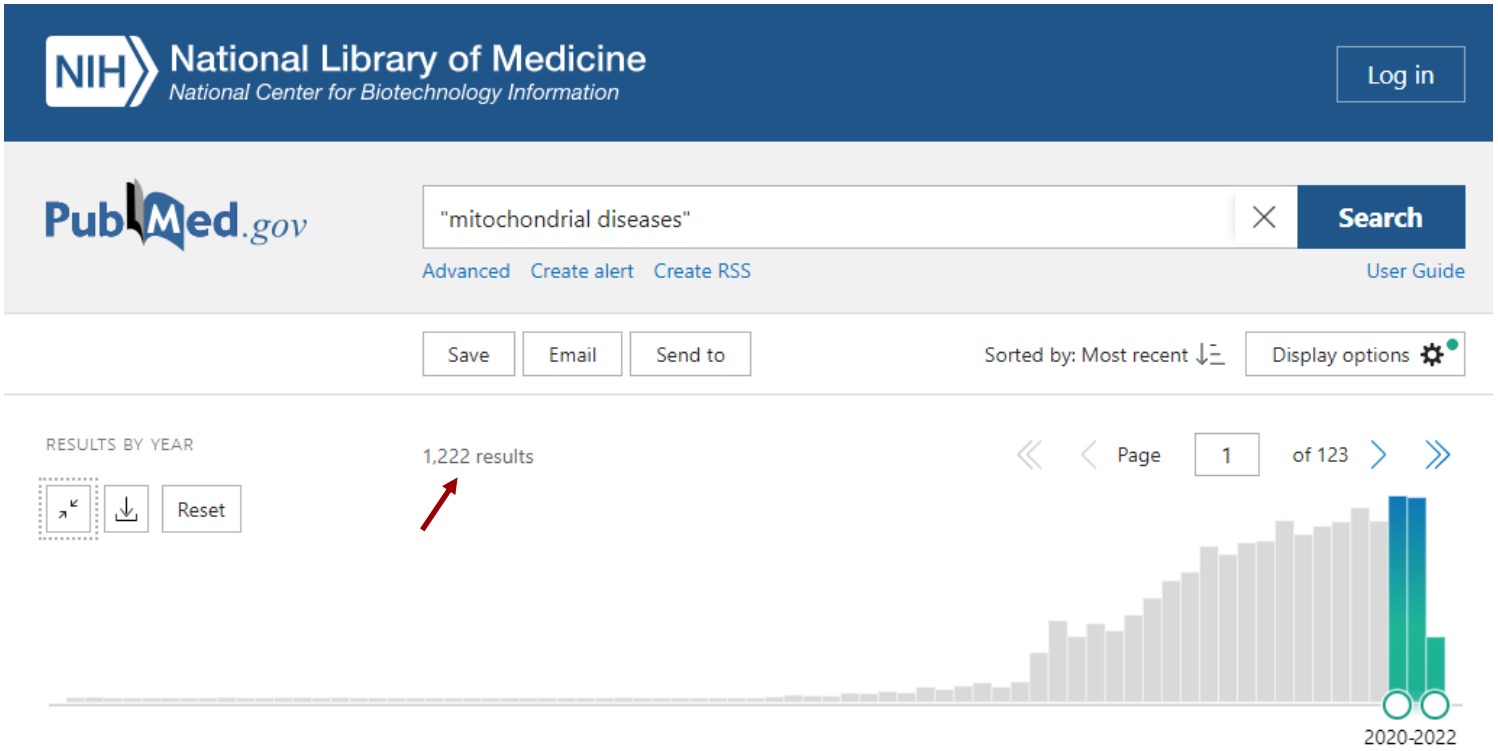
Rolf Luft, MD, PhD (1914-2007)



Chinnery PF, EMBO Molecular Medicine 2015

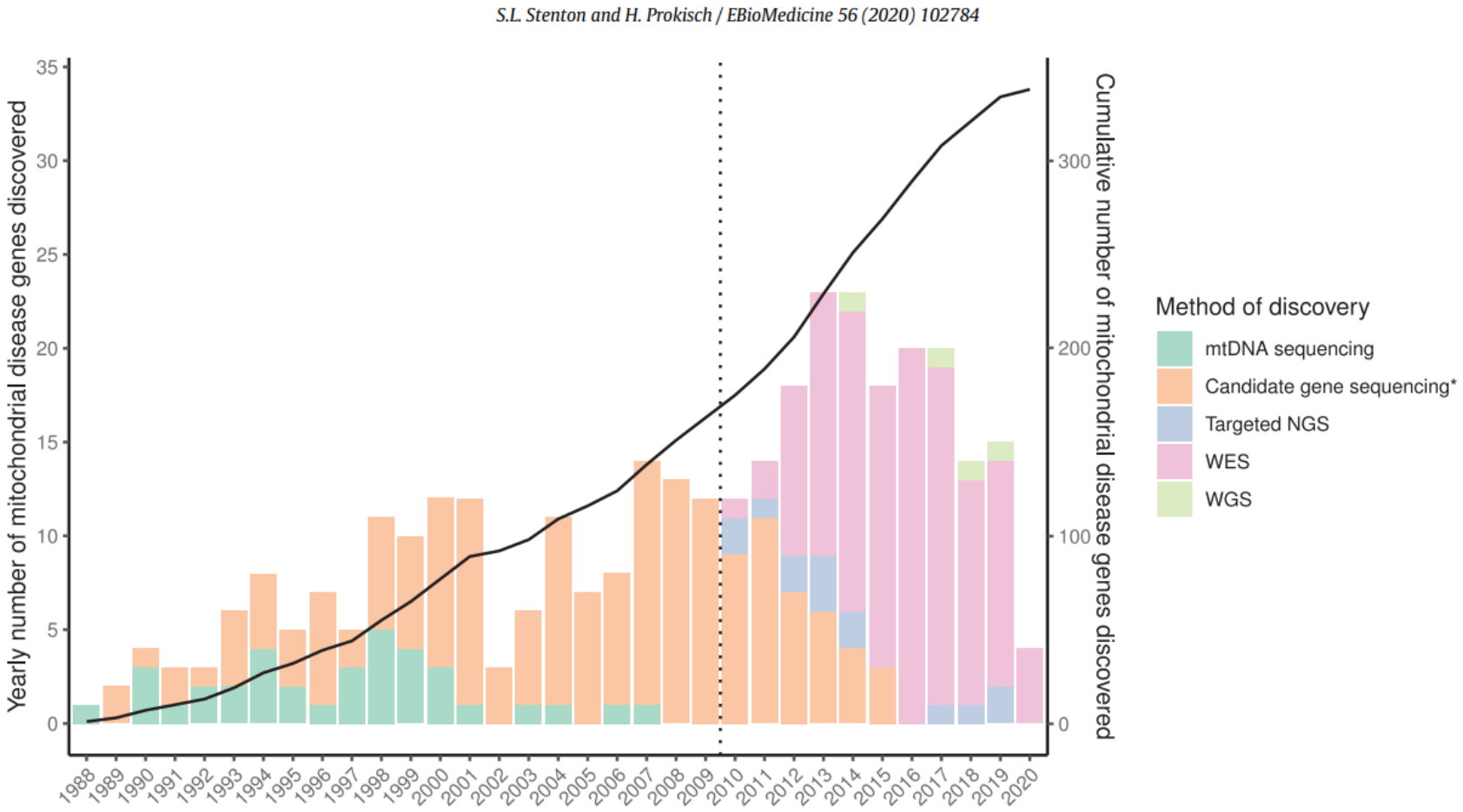
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Mitochondrial Diseases



Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Mitochondrial Diseases



Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Mitochondrial Diseases

Pathogenesis

TISSUE-SPECIFIC STEM CELLS

STEM CEI

Mitochondria in neurogenesis: Implications for mitochondrial diseases

Dario Brunetti[1,2] | Werner Dykstra[3] | Stephanie Le[4] | Annika Zink[4] | Alessandro Prigione[3,4]

Nature **524**, 234–238 (2015)

Metabolic rescue in pluripotent cells from patients with mtDNA disease

Hong Ma[1,2], Clifford D. L. Folmes[3], Jun Wu[4], Robert Morey[5], Sergio Mora-Castilla[5], Alejandro Ocampo[4], Li Ma[4], Joanna Poulton[6], Xinjian Wang[7], Riffat Ahmed[1,2], Eunju Kang[1,2], Yeonmi Lee[1,2], Tomonari Hayama[1,2], Ying Li[1,2], Crystal Van Dyken[1,2], Nuria Marti Gutierrez[1,2], Rebecca Tippner-Hedges[1,2], Amy Koski[1,2], Nargiz Mitalipov[1,2], Paula Amato[8], Don P. Wolf[5], Taosheng Huang[7], Andre Terzic[3], Louise C. Laurent[5], Juan Carlos Izpisua Belmonte[4] & Shoukhrat Mitalipov[1,2]

New Results — Follow this preprint

Human iPSC-derived cerebral organoids model features of Leigh Syndrome and reveal abnormal corticogenesis

Alejandra I. Romero-Morales, Gabriella L. Robertson, Anuj Rastogi, Megan L. Rasmussen, Hoor Temuri, Gregory Scott McElroy, Ram Prosad Chakrabarty, Lawrence Hsu, Paula M. Almonacid, Bryan A. Millis, Navdeep S. Chandel, Jean-Philippe Cartailler, Vivian Gama

doi: https://doi.org/10.1101/2020.04.21.054361

Cell Death and Disease (2020)11:182

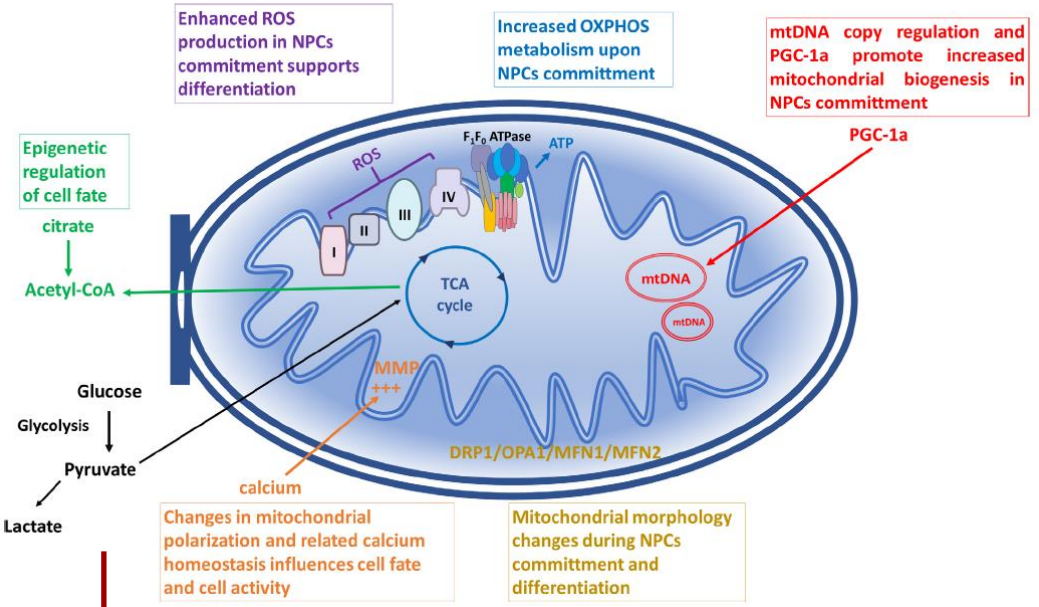
Organoid cultures of MELAS neural cells reveal hyperactive Notch signaling that impacts neurodevelopment

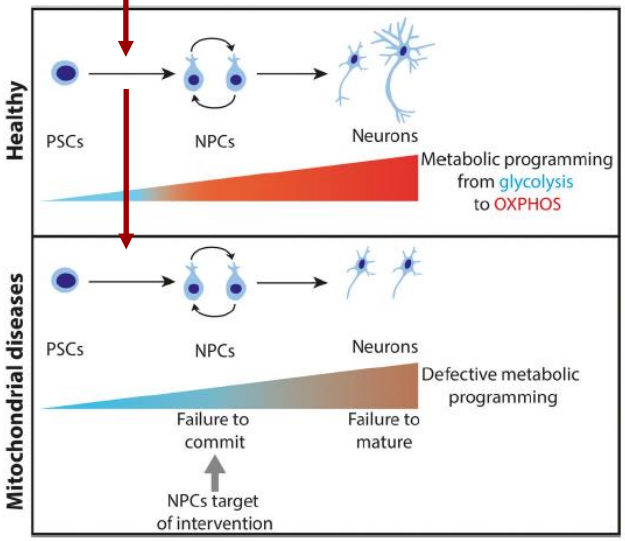
Winanto[1], Zi Jian Khong[1,2], Boon-Seng Soh[1,3,4], Yong Fan[4] and Shi-Yan Ng[1,4,5,6]

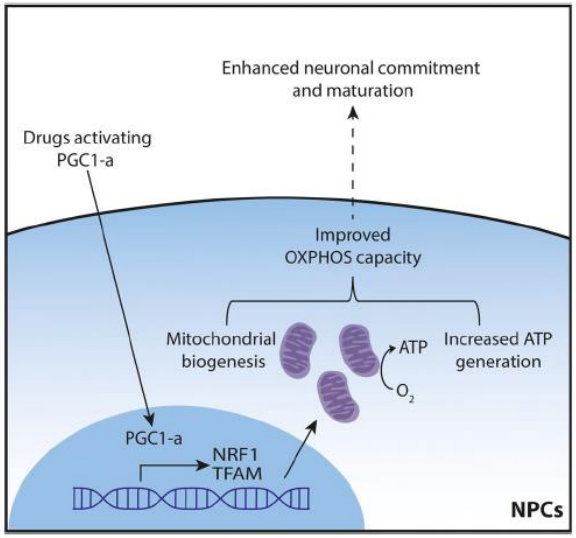
Defective metabolic programming impairs early neuronal morphogenesis in neural cultures and an organoid model of Leigh syndrome

Gizem Inak, Agnieszka Rybak-Wolf, ... Alessandro Prigione + Show authors

Nature Communications **12**, Article number: 1929 (2021) | Cite this article







Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

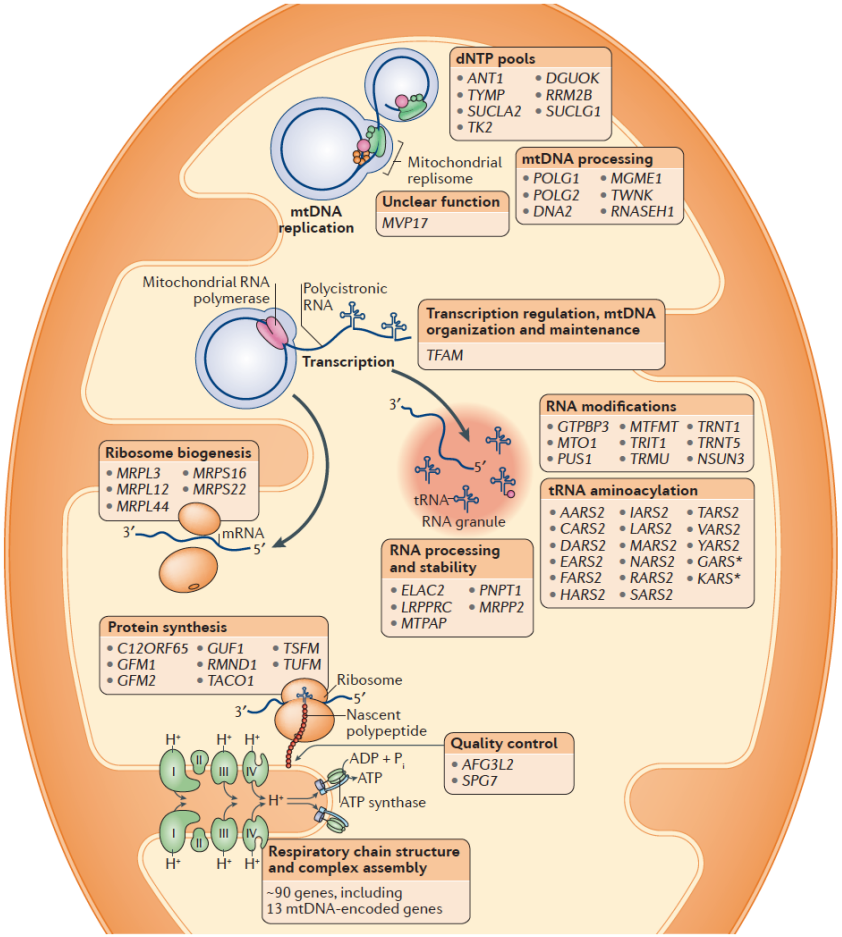
Mitochondrial Diseases

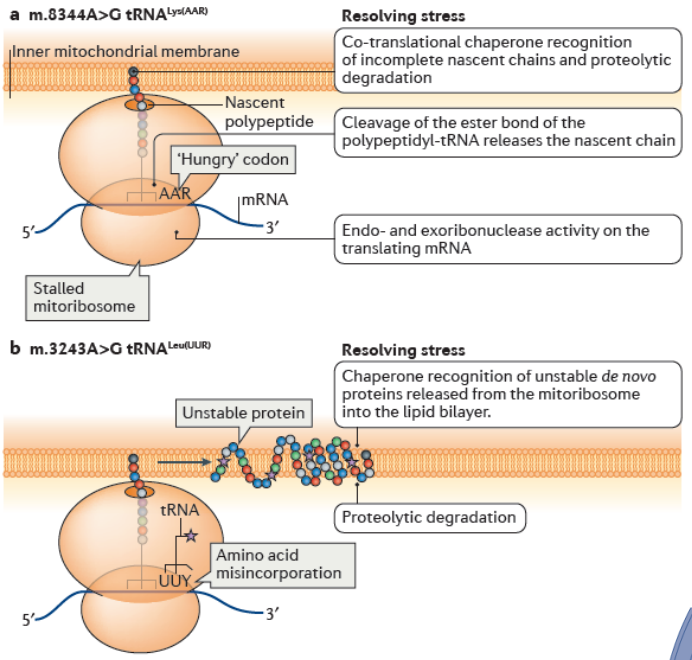
Pathogenesis

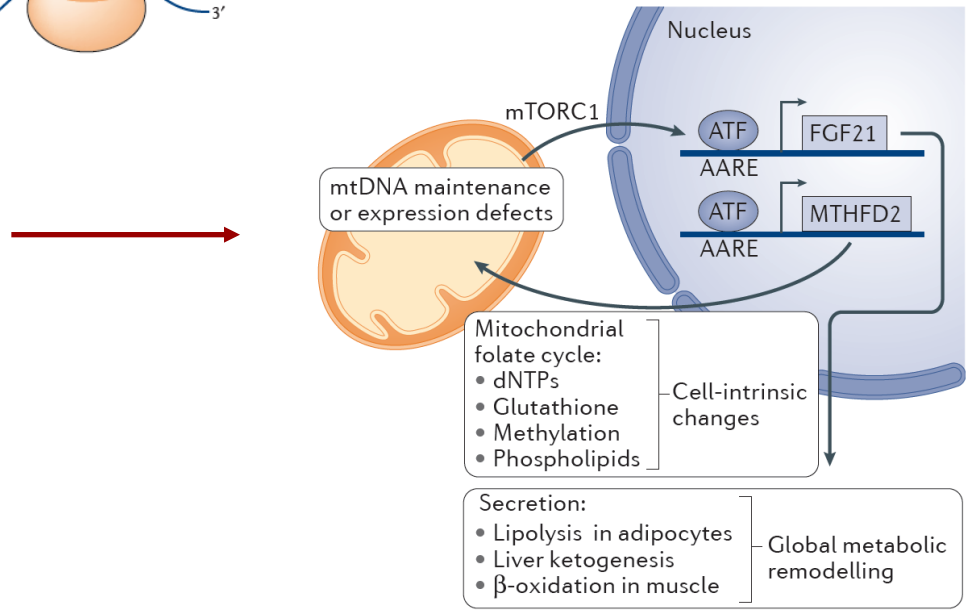
NATURE REVIEWS | MOLECULAR CELL BIOLOGY VOLUME 19 | FEBRUARY 2018

Mitochondrial diseases: the contribution of organelle stress responses to pathology

Anu Suomalainen[1–3] and Brendan J. Battersby[4]

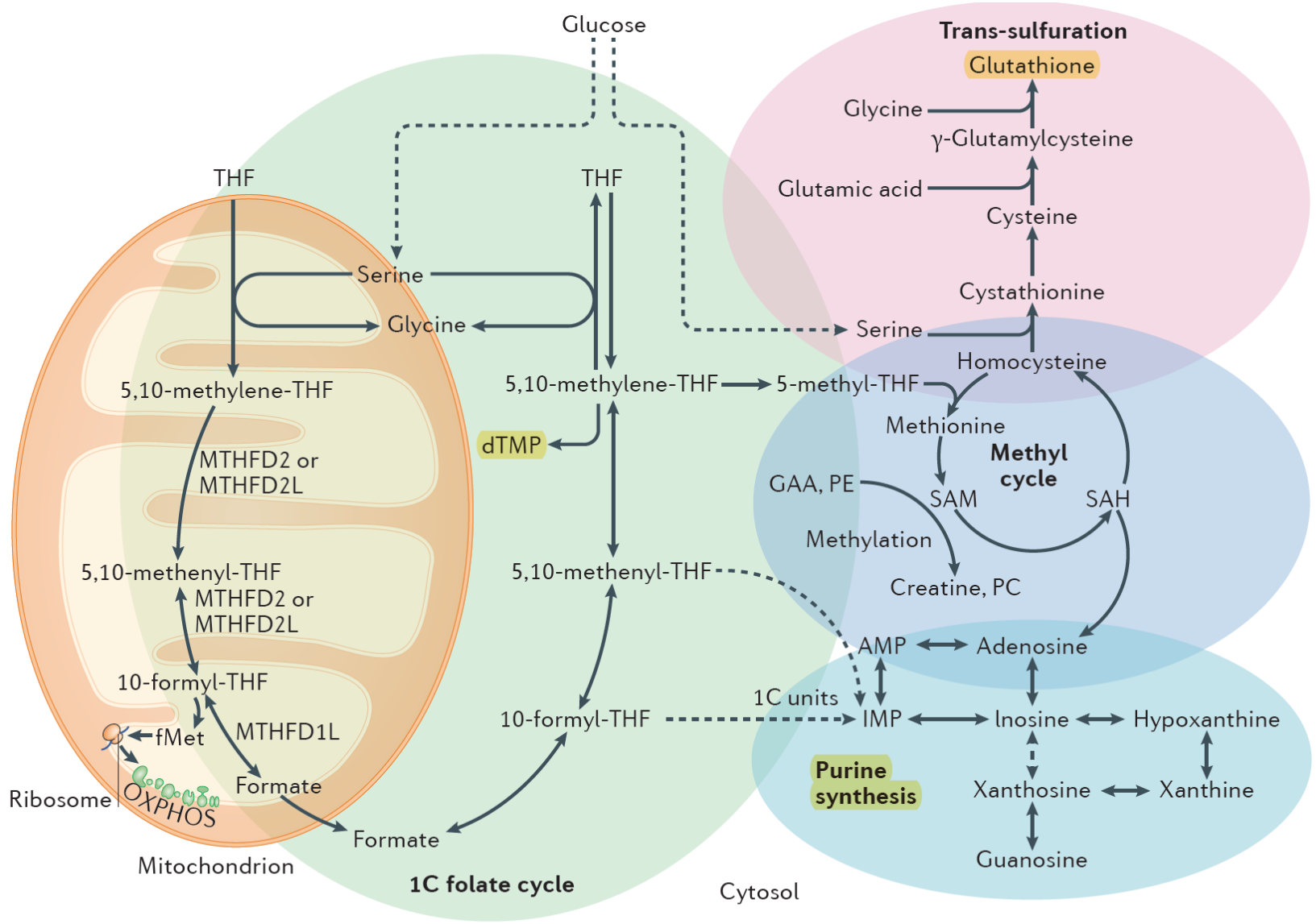






Mitochondrial Diseases

Pathogenesis



dTMP, deoxythymidine monophosphate

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

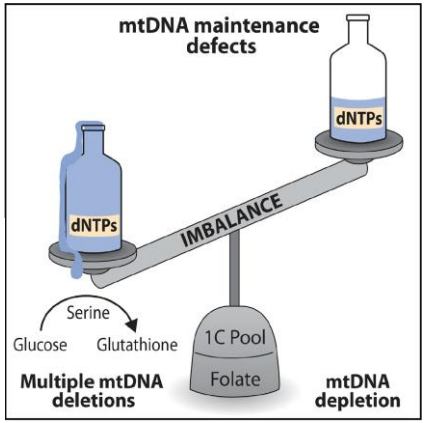
Mitochondrial Diseases

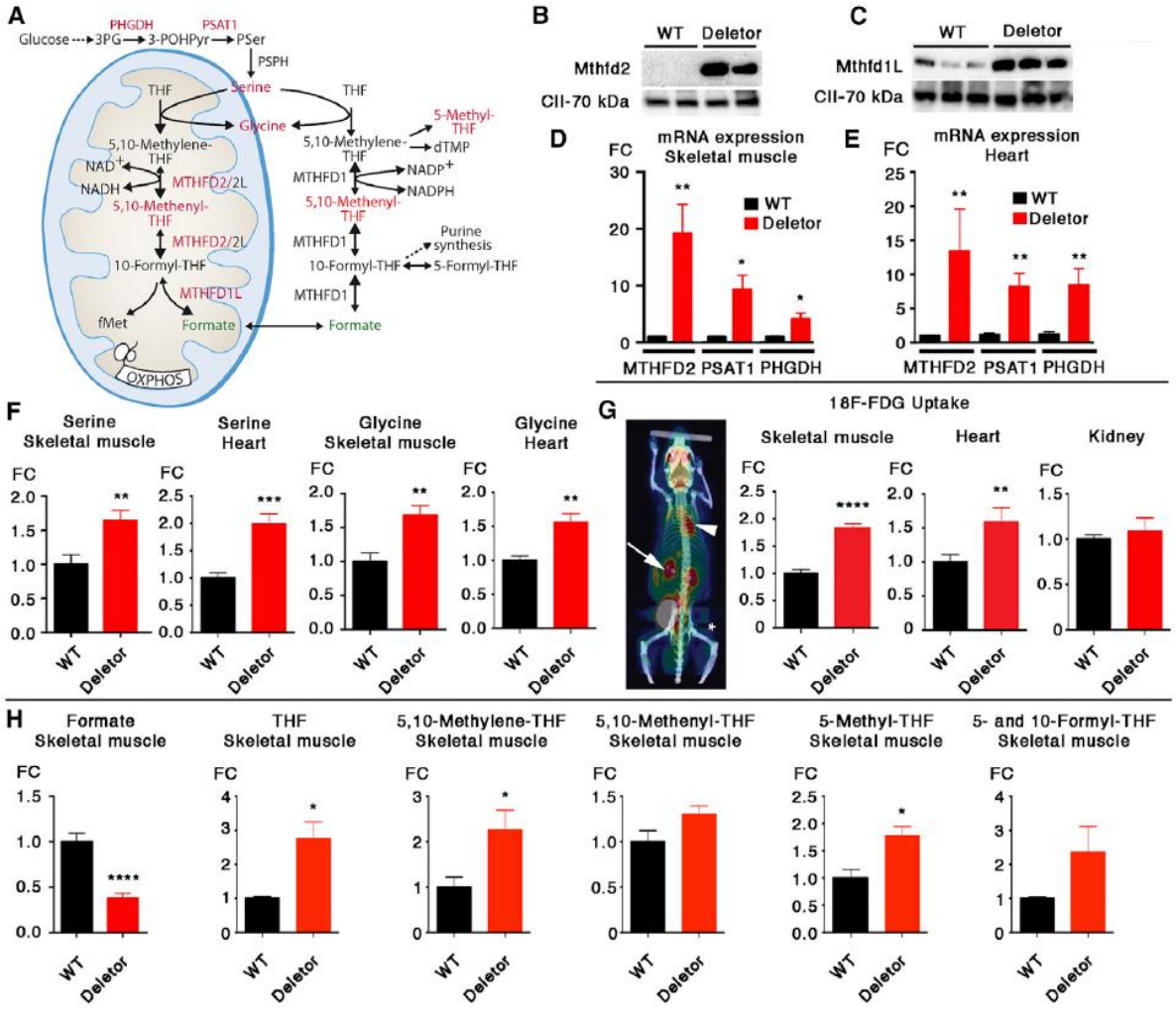
Pathogenesis

Cell Metabolism *23*, 635–648, April 12, 2016

Mitochondrial DNA Replication Defects Disturb Cellular dNTP Pools and Remodel One-Carbon Metabolism

Joni Nikkanen,[1] Saara Forsström,[1] Liliya Euro,[1] Ilse Paetau,[1] Rebecca A. Kohnz,[2] Liya Wang,[3] Dmitri Chilov,[1] Jenni Viinamäki,[4] Anne Roivainen,[5,6] Päivi Marjamäki,[5] Heidi Liljenbäck,[5,6] Sofia Ahola,[1] Jana Buzkova,[1] Mügen Terzioglu,[1] Nahid A. Khan,[1] Sini Pimes-Karhu,[1] Anders Paetau,[7] Tuula Lönnqvist,[8] Antti Sajantila,[4] Pirjo Isohanni,[1,8] Henna Tyynismaa,[1,10] Daniel K. Nomura,[2] Brendan J. Battersby,[1] Vidya Velagapudi,[11] Christopher J. Carroll,[1,*] and Anu Suomalainen[1,9,12,*]

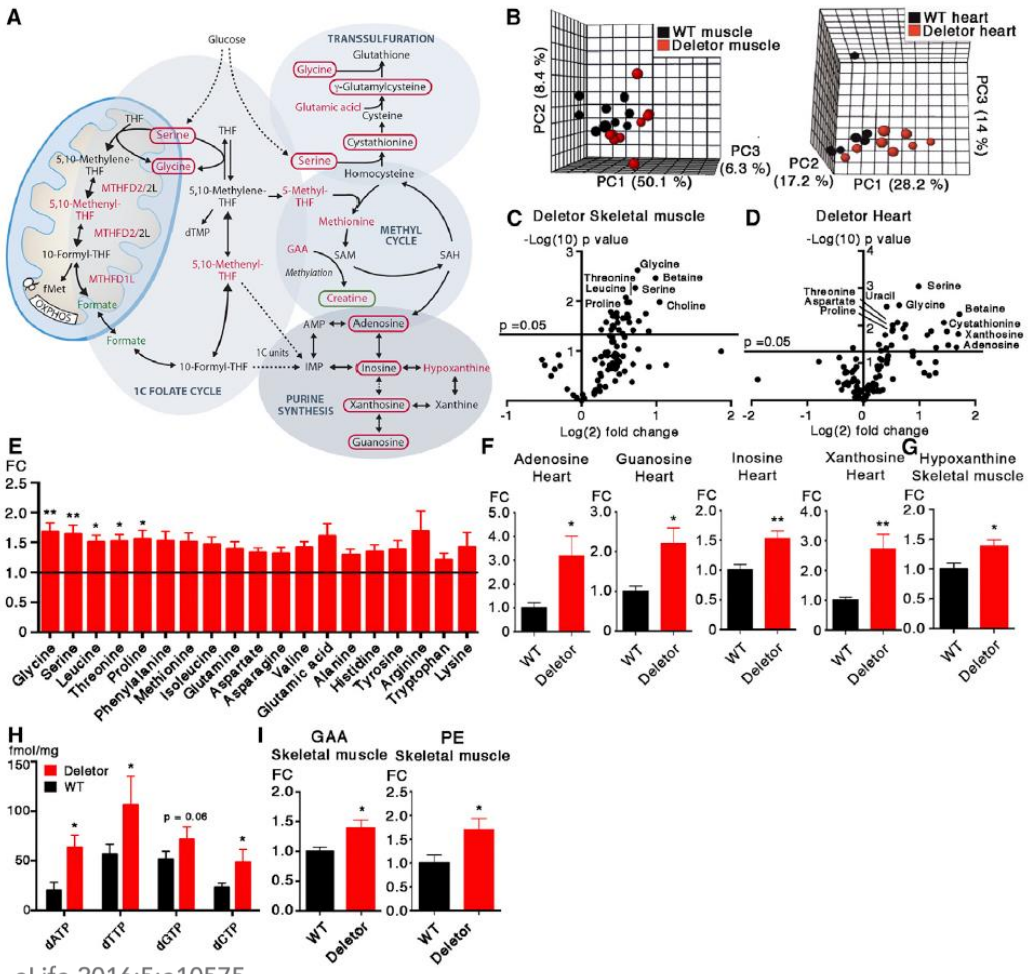




Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Mitochondrial Diseases

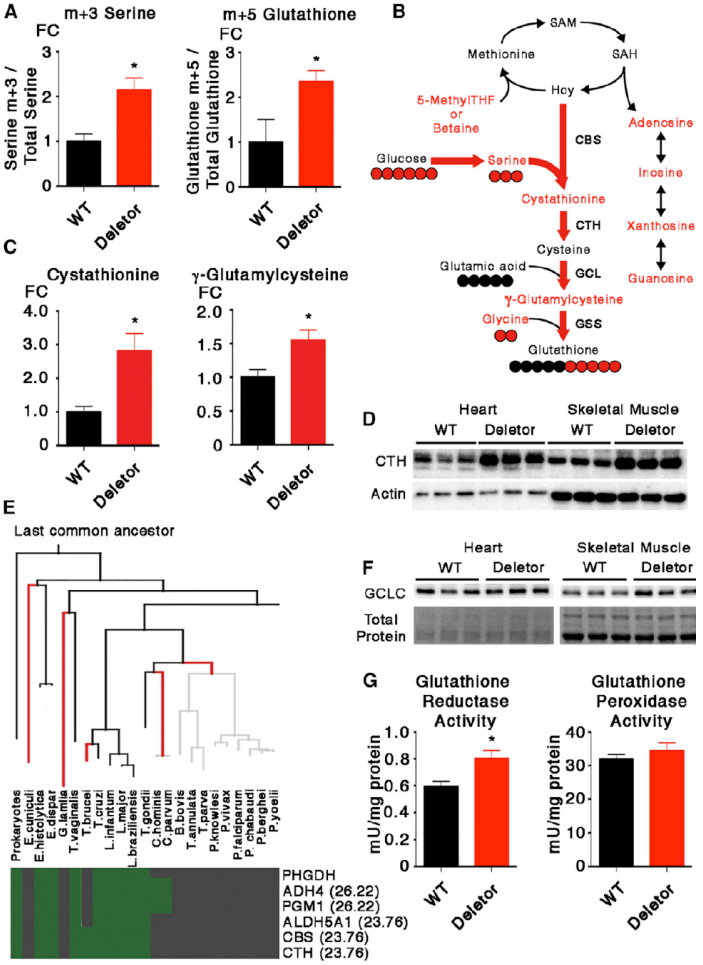
Pathogenesis



eLife 2016;5:e10575.

Mitochondrial dysfunction remodels one-carbon metabolism in human cells

Xiaoyan Robert Bao[1,2,3†], Shao-En Ong[3‡], Olga Goldberger[1], Jun Peng[1,3], Rohit Sharma[1], Dawn A Thompson[3], Scott B Vafai[1,3], Andrew G Cox[4], Eizo Marutani[5], Fumito Ichinose[5], Wolfram Goessling[3,4], Aviv Regev[3,6], Steven A Carr[3], Clary B Clish[3], Vamsi K Mootha[1,2,3*]



Nikkanen J, et al. Cell Metbolism 2016

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Mitochondrial Diseases

Pathogenesis

Article

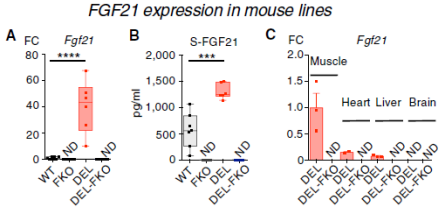
Cell Metabolism

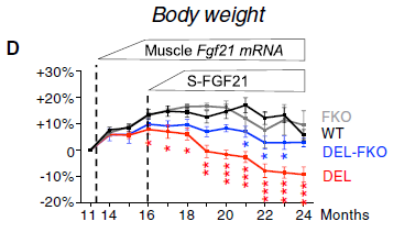
Fibroblast Growth Factor 21 Drives Dynamics of Local and Systemic Stress Responses in Mitochondrial Myopathy with mtDNA Deletions

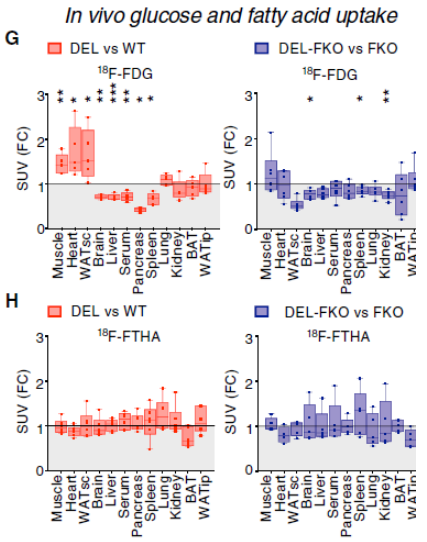
Saara Forsström,[1,11] Christopher B. Jackson,[1,11] Christopher J. Carroll,[1,2] Mervi Kuronen,[1] Eija Pirinen,[3] Swagat Pradhan,[1] Anastasiia Marmyleva,[1] Mari Auranen,[4] Iida-Marja Kleine,[1] Nahid A. Khan,[1] Anne Roivainen,[5,6] Päivi Marjamäki,[5] Heidi Liljenbäck,[5,6] Liya Wang,[7] Brendan J. Battersby,[8] Uwe Richter,[8] Vidya Velagapudi,[9] Joni Nikkanen,[1] Liliya Euro,[1] and Anu Suomalainen[1,4,10,12,*]

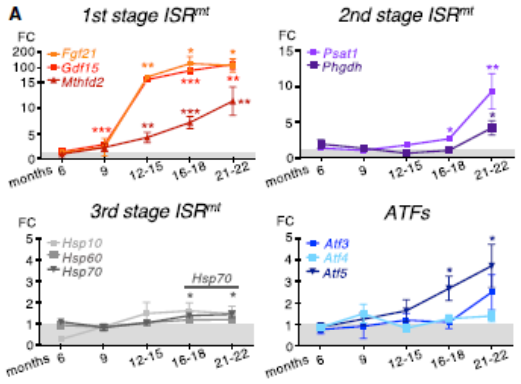
Mitochondrial stress responses are

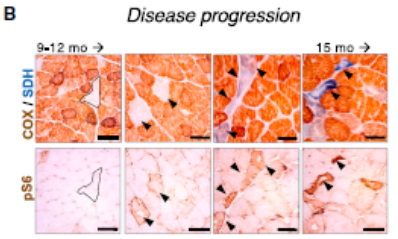
- **only partially conserved in species**
- **not generalizable** between organisms or even mammalian cell types
- **FGF21** is a key mediator of metabolic remodeling and progression of ISRmt locally and systemically

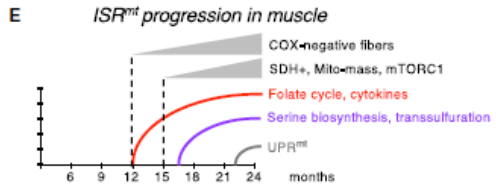


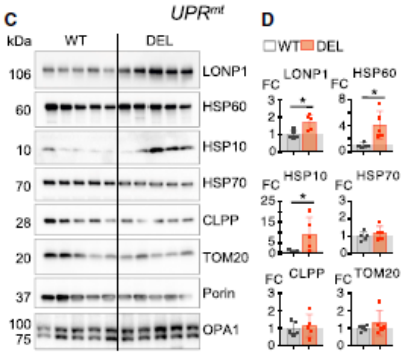


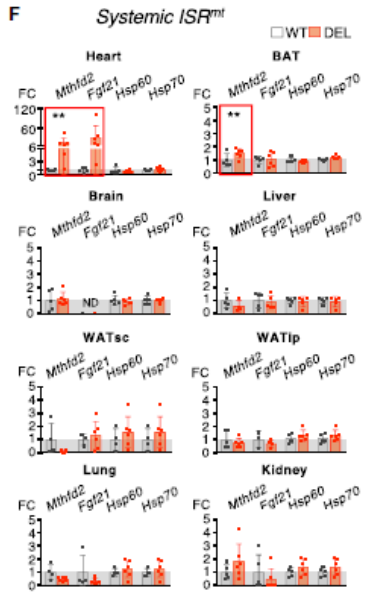


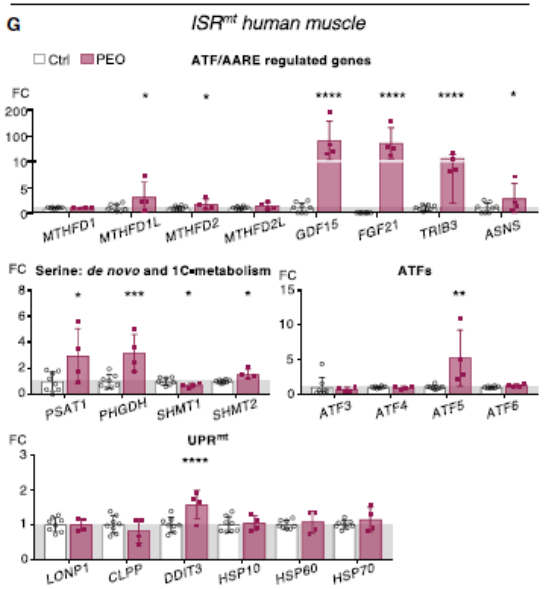












Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Mitochondrial Diseases

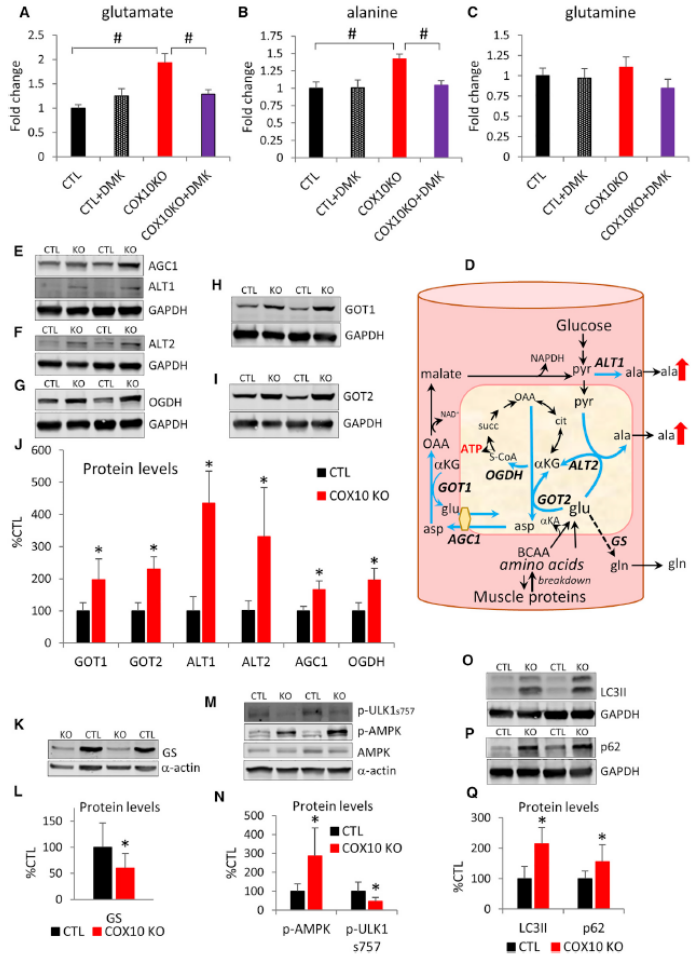
Pathogenesis

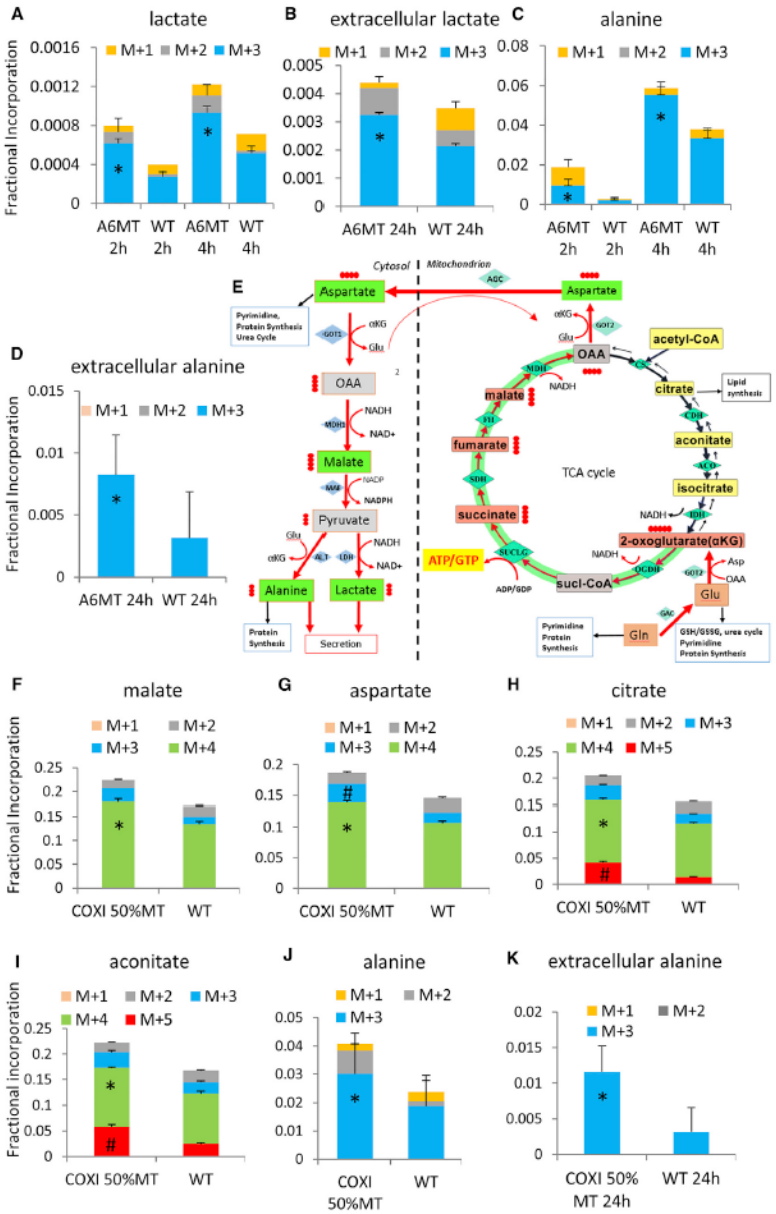
Article

Cell Metabolism

Rewiring of Glutamine Metabolism Is a Bioenergetic Adaptation of Human Cells with Mitochondrial DNA Mutations

Qiuying Chen,[2,8] Kathryne Kirk,[1,8] Yevgeniya I. Shurubor,[1] Dazhi Zhao,[1] Andrea J. Arreguin,[1] Ifrah Shahi,[1] Federica Valsecchi,[1] Guido Primiano,[3] Elizabeth L. Calder,[4] Valerio Carelli,[5,6] Travis T. Denton,[7] M. Flint Beal,[1] Steven S. Gross,[2] Giovanni Manfredi,[1,*] and Marilena D'Aurelio[1,9,*]





Gemelli
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Biomarkers

Lancet Neurol 2011; 10: 806–18

FGF-21 as a biomarker for muscle-manifesting mitochondrial respiratory chain deficiencies: a diagnostic study

ANN NEUROL 2015;78:814–823

Growth Differentiation Factor 15 as a Useful Biomarker for Mitochondrial Disorders

ANNALS of Clinical and Translational Neurology
Open Access
AMERICAN NEUROLOGICAL ASSOCIATION
INNOVATORS IN DISCOVERY, EDUCATION, AND CARE

RESEARCH ARTICLE

Accuracy of FGF-21 and GDF-15 for the diagnosis of mitochondrial disorders: A meta-analysis

Yan Lin[1], Kunqian Ji[1], Xiaotian Ma[2], Shuangwu Liu[1], Wei Li[1], Yuying Zhao[1] & Chuanzhu Yan[1,2,3]

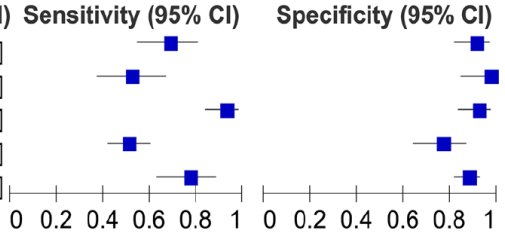
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Biomarkers

	Estimates (95% CI)	
	FGF-21	GDF-15
Number of included studies	5	7
Number of subjects	718	845
Sensitivity	0.71 (0.53, 0.84)	0.83 (0.65, 0.92)
Specificity	0.88 (0.82, 0.93)	0.92 (0.84, 0.96)
Positive likelihood ratio	6.10 (3.40, 10.70)	9.90 (4.60, 21.20)
Negative likelihood ratio	0.33 (0.19, 0.58)	0.19 (0.08, 0.42)
Diagnostic odds ratio	18.00 (6.00, 54.00)	52.00 (13.00, 205.00)
AUC	0.90 (0.87, 0.92)	0.94 (0.92, 0.96)

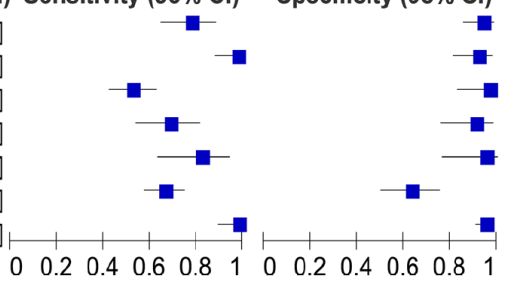
A. FGF-21

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Davis RL (2016)	37	6	17	60	0.69 [0.54, 0.80]	0.91 [0.81, 0.97]
Montero R (2016)	25	1	23	32	0.52 [0.37, 0.67]	0.97 [0.84, 1.00]
Suomalainen A (2011)	62	6	5	68	0.93 [0.83, 0.98]	0.92 [0.83, 0.97]
Tsygankova PG (2019)	62	14	60	46	0.51 [0.42, 0.60]	0.77 [0.64, 0.87]
Yatsuga S (2015)	37	18	11	128	0.77 [0.63, 0.88]	0.88 [0.81, 0.93]



B. GDF-15

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Davis RL (2016)	42	4	12	62	0.78 [0.64, 0.88]	0.94 [0.85, 0.98]
Ji X (2016)	41	4	1	46	0.98 [0.87, 1.00]	0.92 [0.81, 0.98]
Koene S (2015)	51	1	46	29	0.53 [0.42, 0.63]	0.97 [0.83, 1.00]
Montero R (2016)	33	3	15	30	0.69 [0.54, 0.81]	0.91 [0.76, 0.98]
Poulsen NS (2019)	23	1	5	20	0.82 [0.63, 0.94]	0.95 [0.76, 1.00]
Tsygankova PG (2019)	81	22	41	38	0.66 [0.57, 0.75]	0.63 [0.50, 0.75]
Yatsuga S (2015)	47	7	1	139	0.98 [0.89, 1.00]	0.95 [0.90, 0.98]



Lin Y, et al. 2020

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

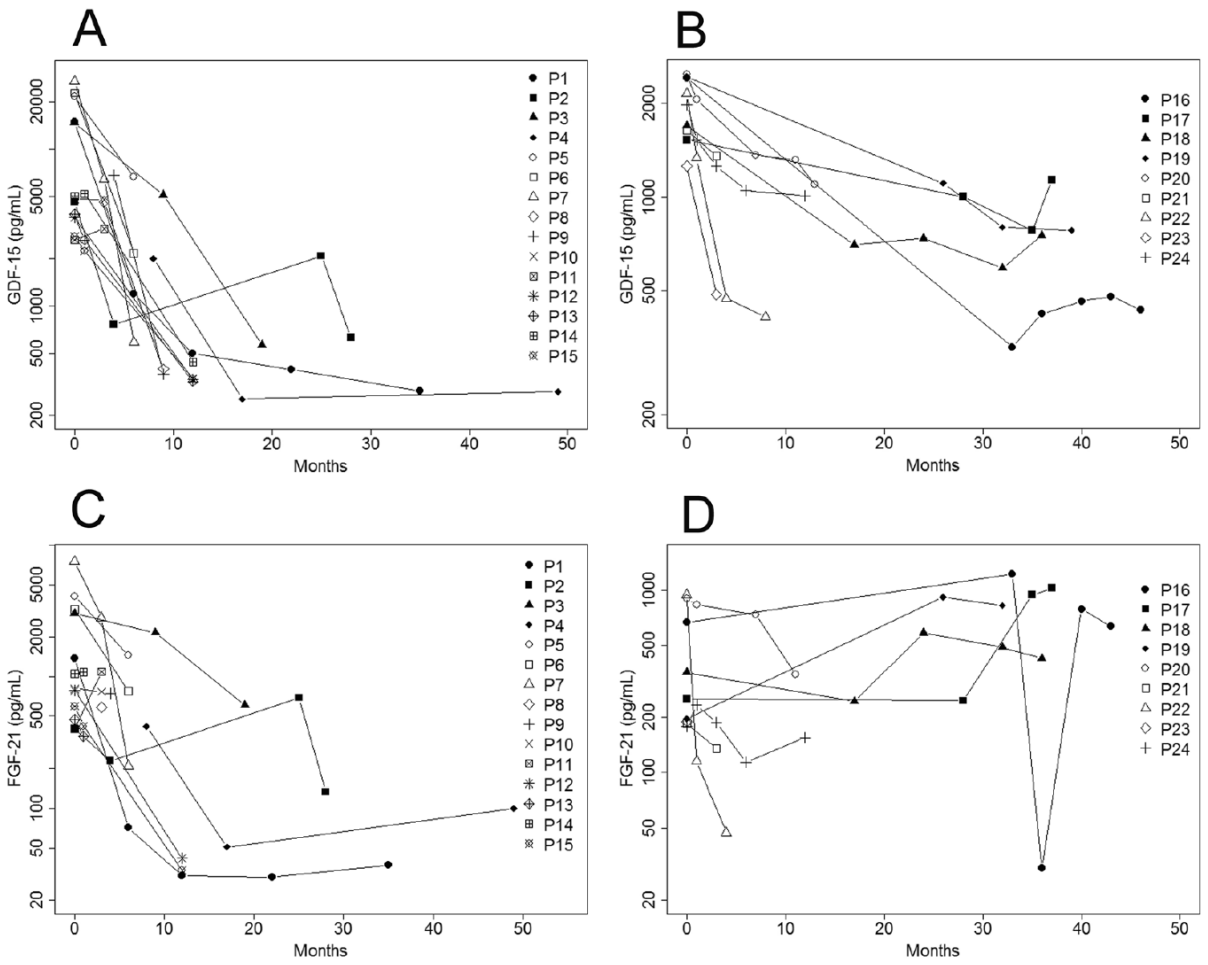
Biomarkers

SCIENTIFIC REPORTS | (2020) 10:10111

Growth Differentiation Factor 15 is a potential biomarker of therapeutic response for TK2 deficient myopathy

Cristina Dominguez-Gonzalez[1,2,3], Carmen Badosa[4], Marcos Madruga-Garrido[5], Itxaso Martí[6], Carmen Paradas[7,8], Carlos Ortez[4], Jordi Diaz-Manera[3,9], Andres Berardo[1] Jorge Alonso-Pérez[9], Selena Trifunov[4], Daniel Cuadras[11], Susana G. Kalko[12], Cora Blázq Bermejo[3,13], Yolanda Cámara[3,13], Ramon Martí[3,13], Fabiola Mavillard[7,8], Miguel A. Martí Julio Montoya[3,14], Eduardo Ruiz-Pesini[3,14], Joan Villarroya[15,16], Raquel Montero[3,17], Francesc Villarroya[15,16], Rafael Artuch[3,17], Michio Hirano[10], Andrés Nascimento[3,4] & Cecilia Jimenez-Mallebrera[3,4,18] ✉

- **24 patients** with TK2 defciency
- Signifcant correlation between basal GDF-15 and **6MWT**
- During treatments with oral deoxynucleosides, **GDF15 significantly declined**



Gemelli

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Biomarkers

ORIGINAL ARTICLE

JIMD SSIEM WILEY

Diagnostic value of serum biomarkers FGF21 and GDF15 compared to muscle sample in mitochondrial disease

Jenni M. Lehtonen[1] | Mari Auranen[1,2] | Niklas Darin[3] | Kalliopi Sofou[3] | Laurence Bindoff[4,5] | Omar Hikmat[4,6] | Johanna Uusimaa[7] | Päivi Vieira[7] | Már Tulinius[3] | Tuula Lönnqvist[8] | Irenaeus F. de Coo[9,10] | Anu Suomalainen[1,11] | Pirjo Isohanni[1,8]

- **194 suspected mitochondrial disorders** (88 children and 106 adults)
- **FGF21 and GDF15 identified 62%** of patients with genetically verified MD (**82% muscle manifesting**)
- Serum biomarkers pointed to mitochondrial disease in **69% patients who had no diagnostic findings in the muscle sample**
- **FGF21 and GDF15** was highly restricted to **muscle-manifesting mitochondrial diseases** caused by mitochondrial translation defect or mtDNA deletions
- FGF21 and GDF15 together as **first-line diagnostic tools in patients with muscle involvement**; they can be used in all patients with a suspicion of mitochondrial disease, although in pure encephalopathies biomarkers often remain normal
- Analysis of serum biomarkers complement but **do not entirely remove the need for muscle biopsy**
- Biomarkers might be useful in **evaluation of genetic findings**, for example, variants of unknown significance

Biomarkers

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

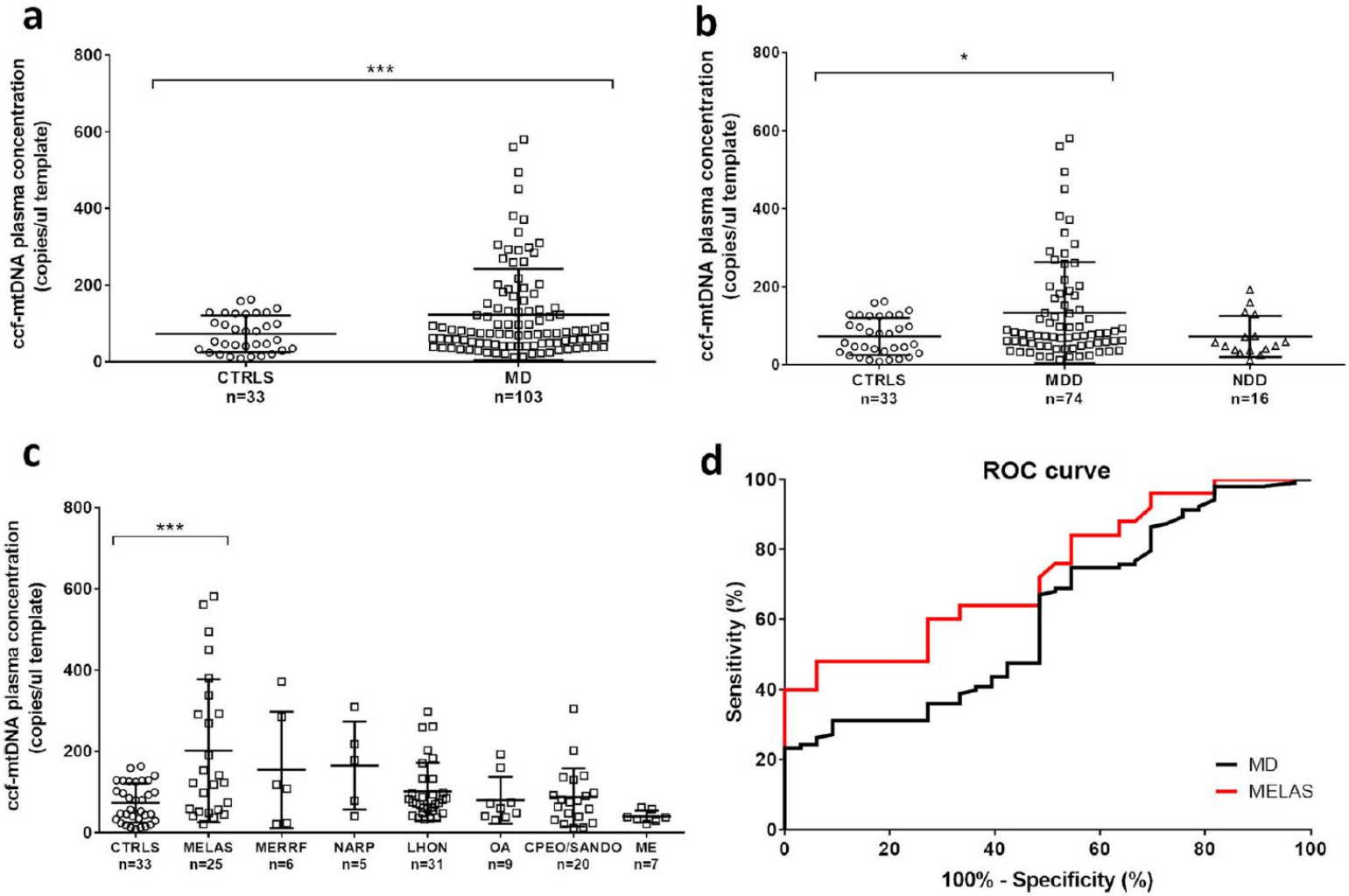
Journal of Molecular Medicine (2020) 98:1467–1478
https://doi.org/10.1007/s00109-020-01967-y

JMolMed

ORIGINAL ARTICLE

Expanding and validating the biomarkers for mitochondrial diseases

Alessandra Maresca[1] · Valentina Del Dotto[2] · Martina Romagnoli[1] · Chiara La Morgia[1,2] · Lidia Di Vito[1] · Mariantonietta Capristo[1] · Maria Lucia Valentino[1,2] · Valerio Carelli[1,2] · the ER-MITO Study Group



Gemelli

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

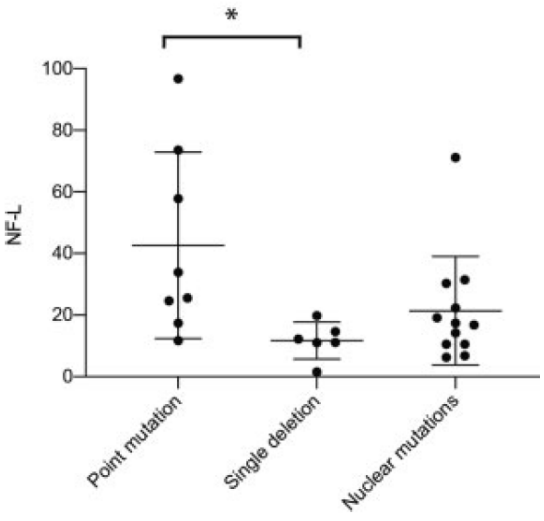
Biomarkers

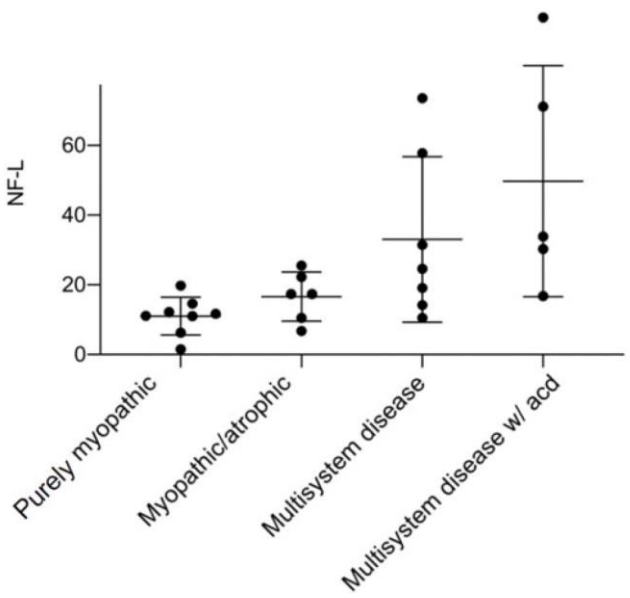
BRAIN COMMUNICATIONS 2021:

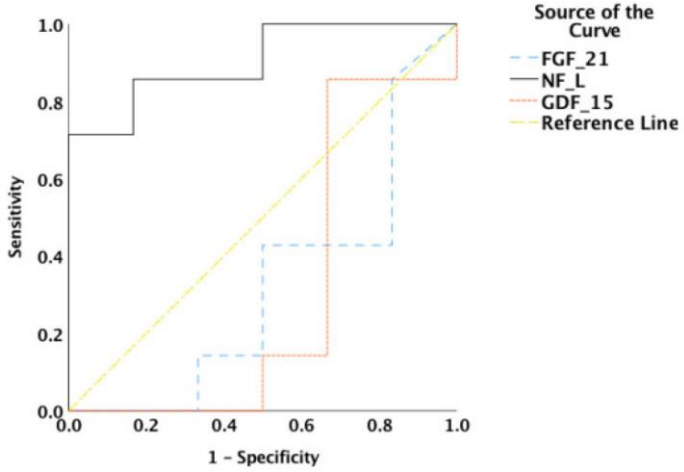
Serum biomarkers in primary mitochondrial disorders

Kristin N. Varhaug,[1,2] Omar Hikmat,[2,3] Hanne Linda Nakkestad,[1,4] Christian A. Vedeler[1,2,4] and Laurence A. Bindoff[1,2,4]

	MtDNA point mutations	N	Single deletions	Nuclear gene mutations	N
Genetic diagnose	*8344 A>G*	2		*POLG*	7
	3243 A>G	4		*TWINKL*	2
	13271 T>C	1		*PITRM1*	1
	5556 G>C	1		*DHX30*	1
				ICSU	1
Age (mean years)	58		43	47	
Gender (female %)	63 %		100 %	83 %	
Total		8	6		12







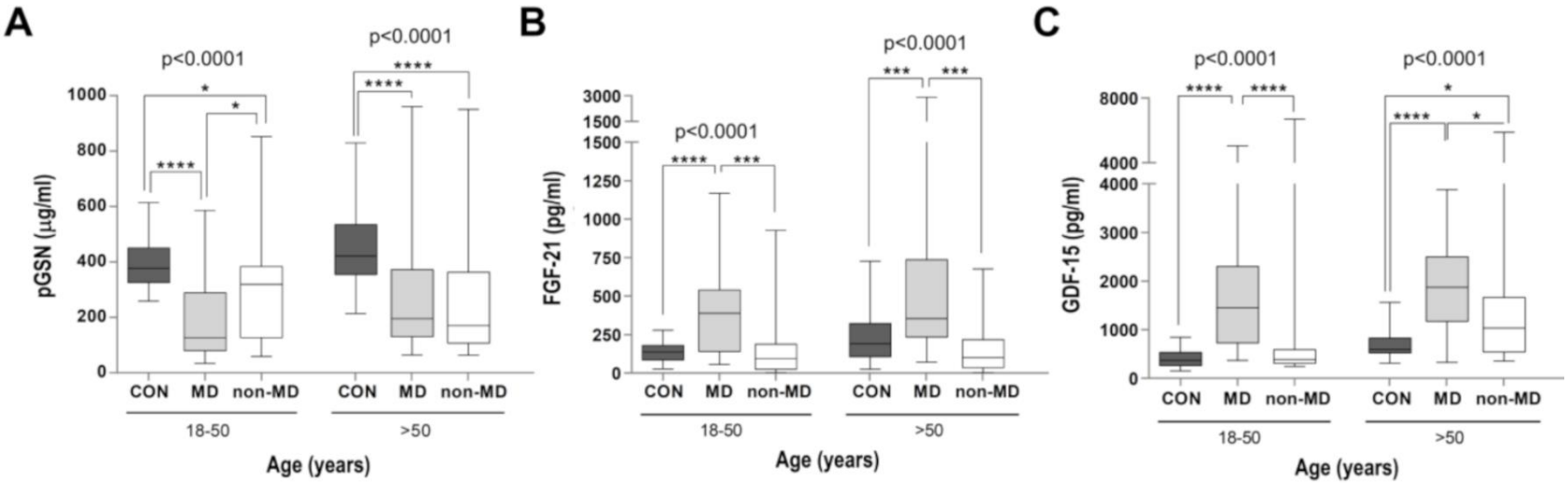
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

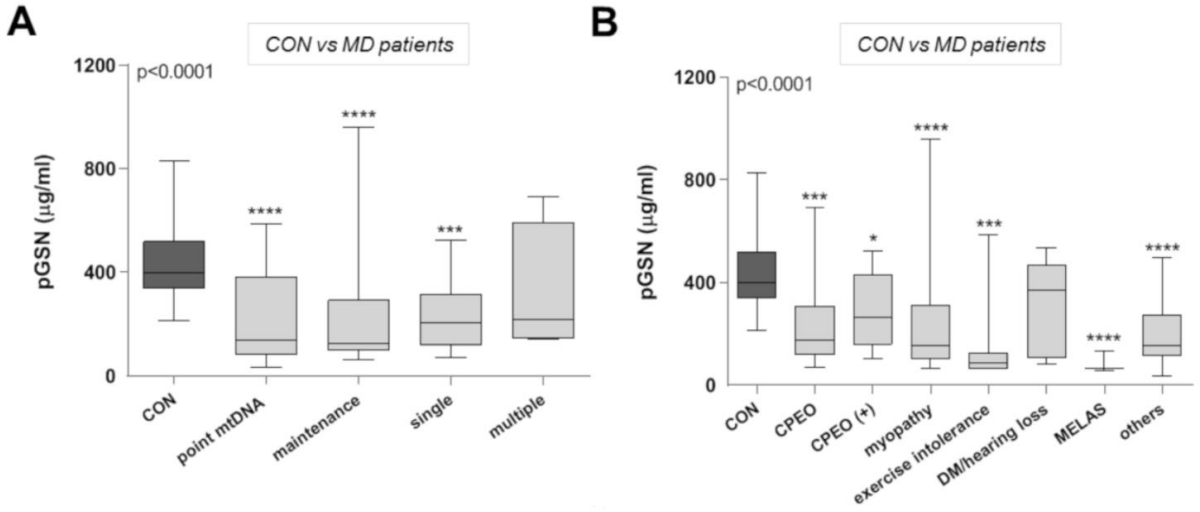
Biomarkers

Int. J. Mol. Sci. **2021**, *22*, 6396.
Article

Plasma Gelsolin Reinforces the Diagnostic Value of FGF-21 and GDF-15 for Mitochondrial Disorders

Ana Peñas [1], Miguel Fernández-De la Torre [1], Sara Laine-Menéndez [1], David Lora [2,3,4], María Illescas [1], Alberto García-Bartolomé [1], Montserrat Morales-Conejo [1,5,6], Joaquín Arenas [1,6], Miguel A. Martín [1,6,7], María Morán [1,6], Cristina Domínguez-González [1,6,8,*] and Cristina Ugalde [1,6,*]





Gemelli

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

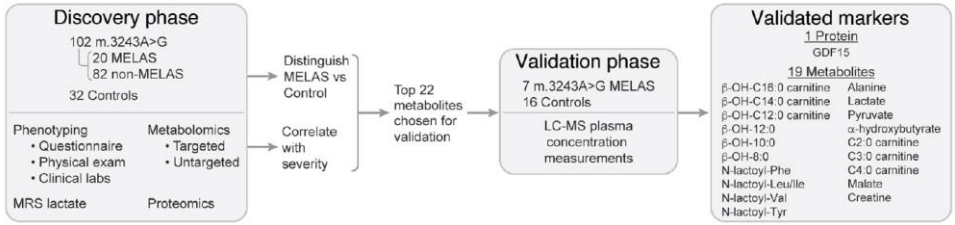
Biomarkers

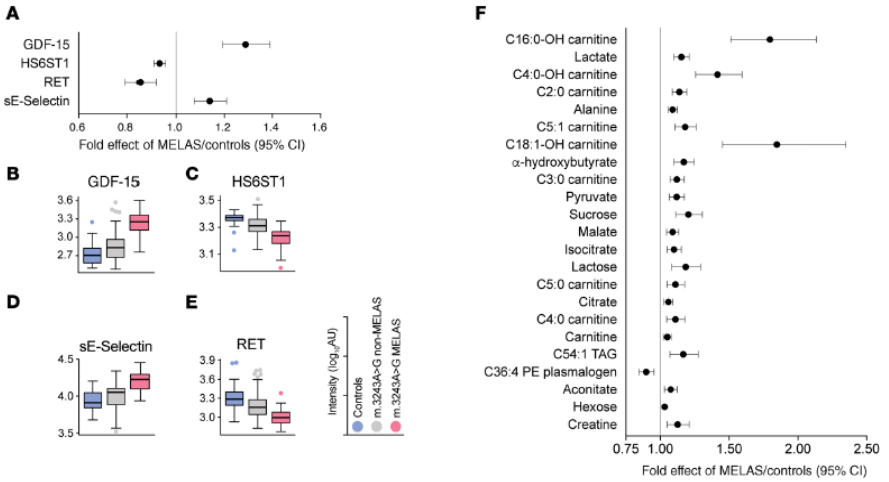
The Journal of Clinical Investigation

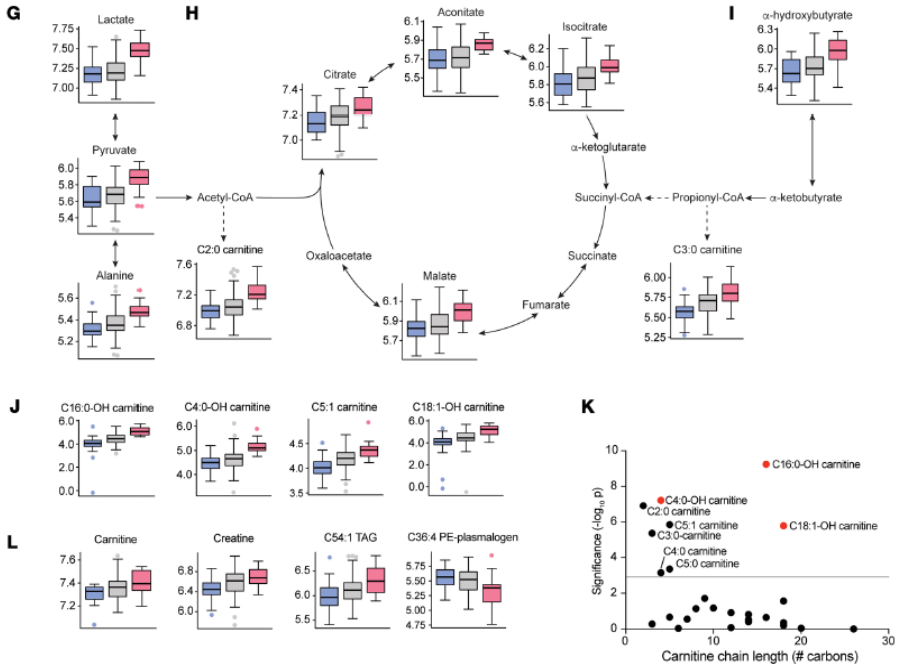
RESEARCH ARTICLE

Circulating markers of NADH-reductive stress correlate with mitochondrial disease severity

Rohit Sharma,[1,2,3,4] Bryn Reinstadler,[1,2,3,4] Kristin Engelstad,[5] Owen S. Skinner,[1,2,3,4] Erin Stackowitz,[5] Ronald G. Haller,[6,7] Clary B. Clish,[4] Kerry Pierce,[4] Melissa A. Walker,[1,2,3,4,8] Robert Fryer,[5] Devin Oglesbee,[9] Xiangling Mao,[10] Dikoma C. Shungu,[10] Ashok Khatri,[11] Michio Hirano,[5] Darryl C. De Vivo,[5] and Vamsi K. Mootha[1,2,3,4]



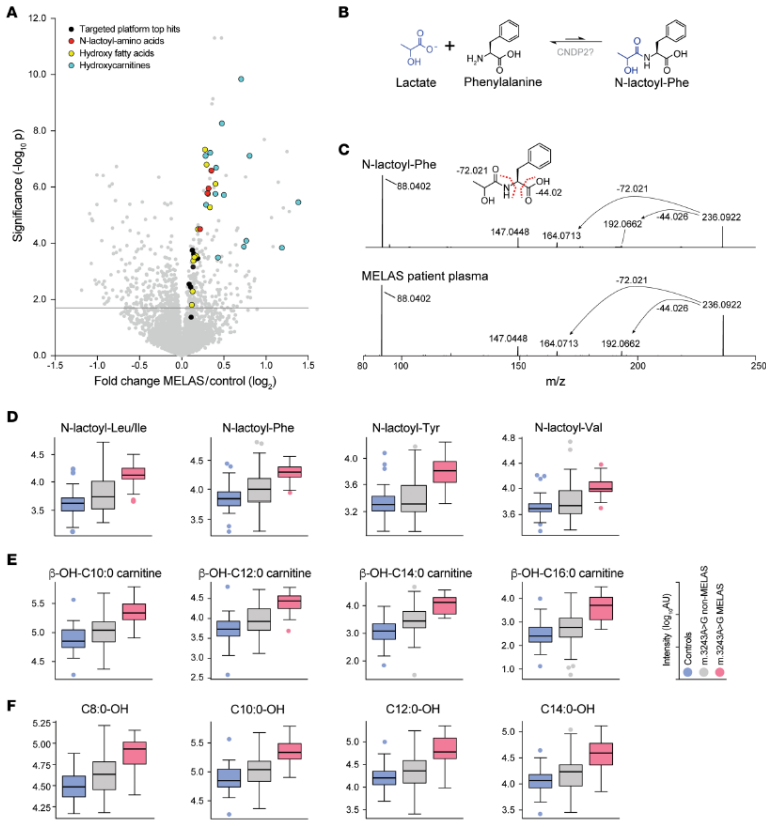




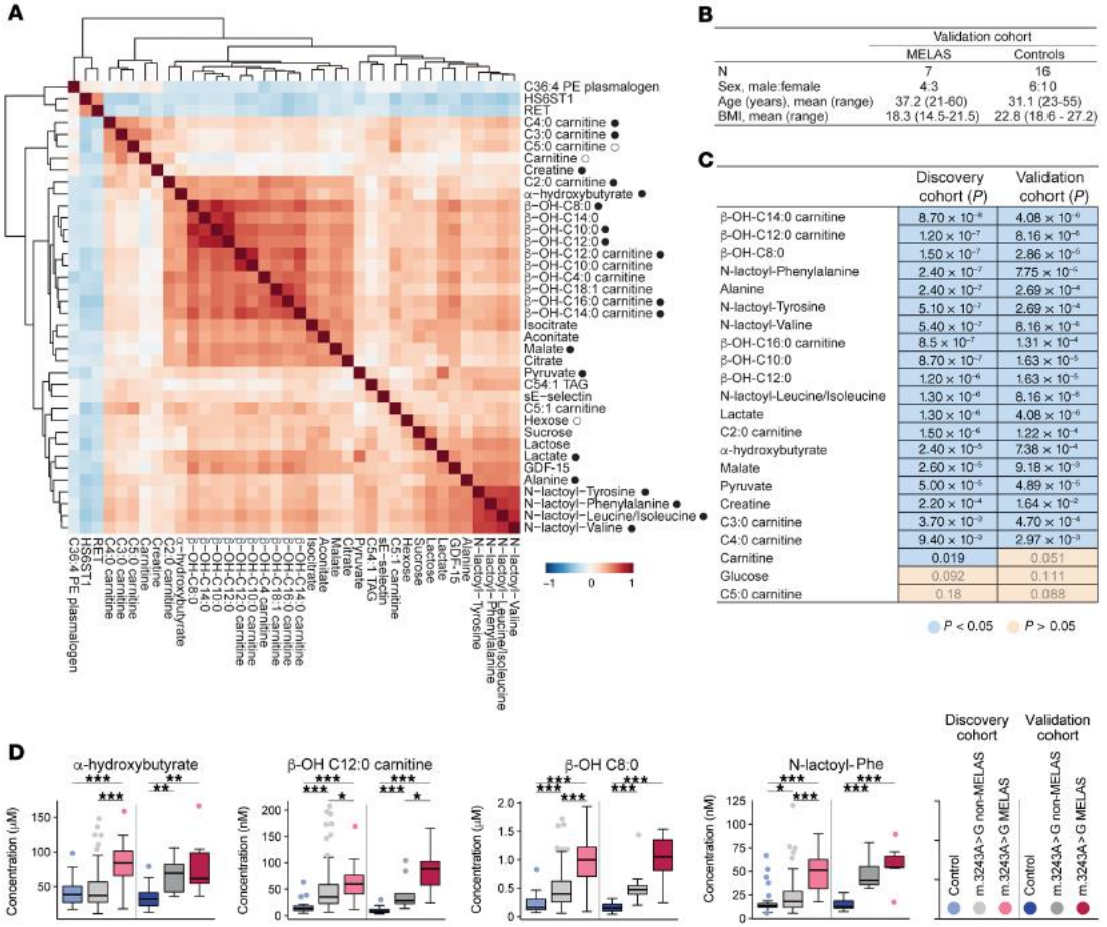
Comparison of 1310 proteins and 376 targeted metabolites in plasma of patients with MELAS and controls.

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Biomarkers



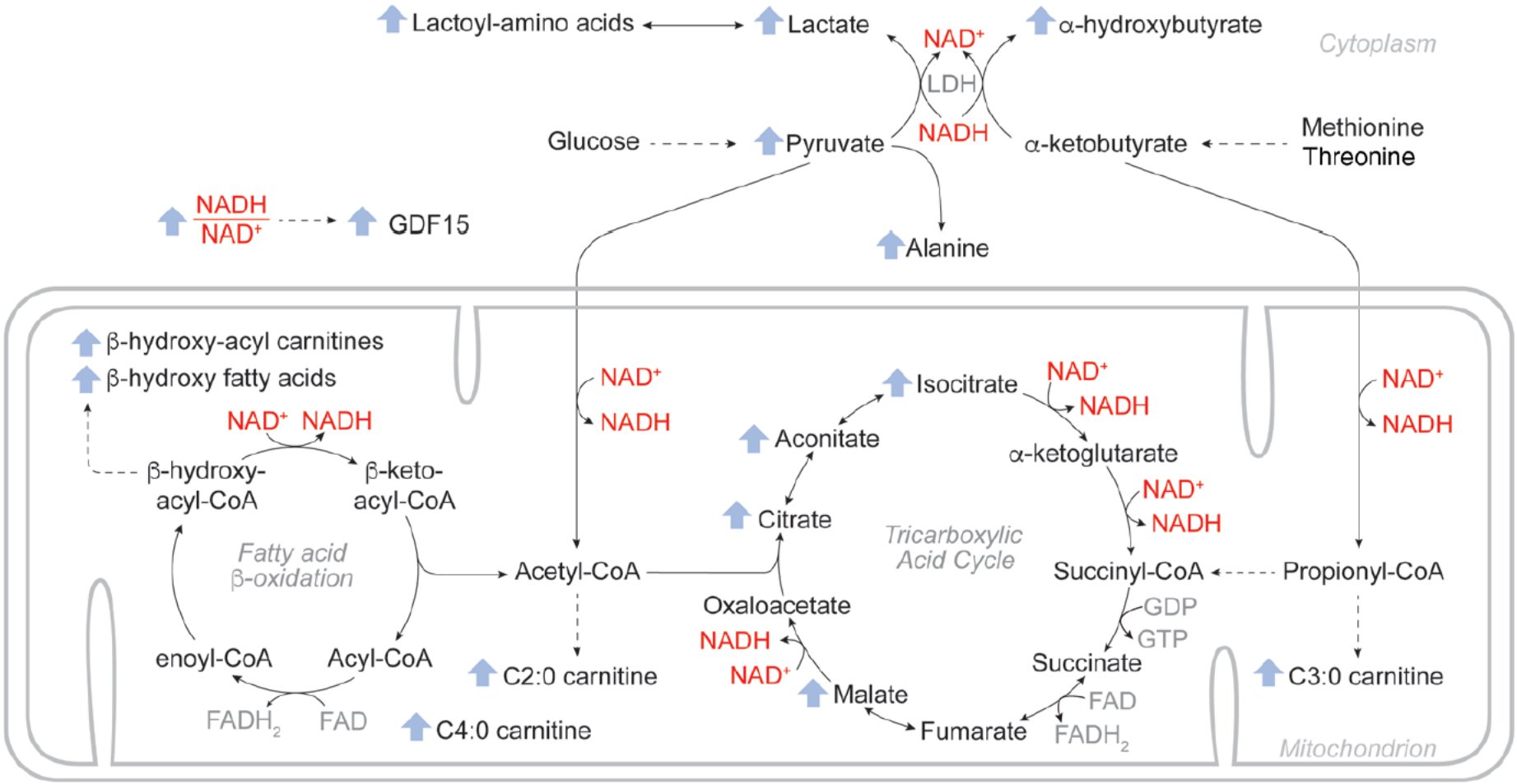
Biomarker discovery from untargeted metabolic profiling



Correlations among most discriminating analytes and validation of top metabolites

Sharma R, et al. 2021

Biomarkers



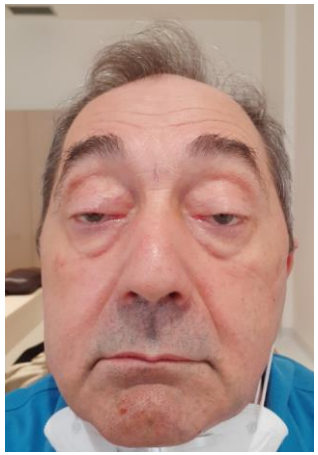
NADH-reductive stress drives the metabolic signature in MELAS.

Sharma R, et al. 2021

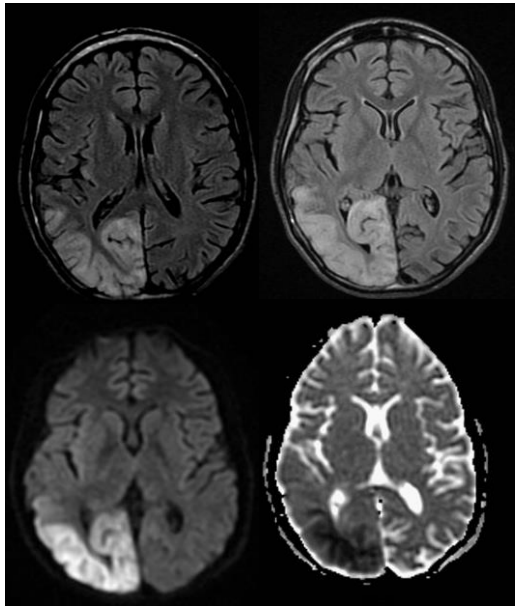
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Classical mitochondrial syndromes

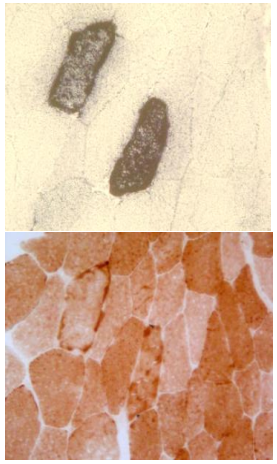
PEO spectrum/Kearns–Sayre syndrome



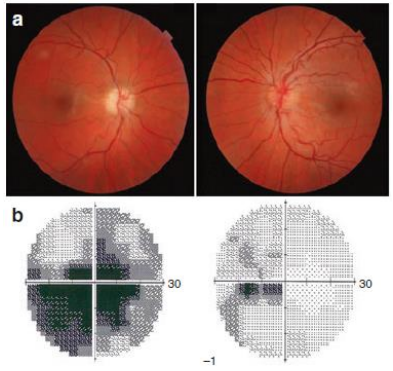
MELAS



MIDD

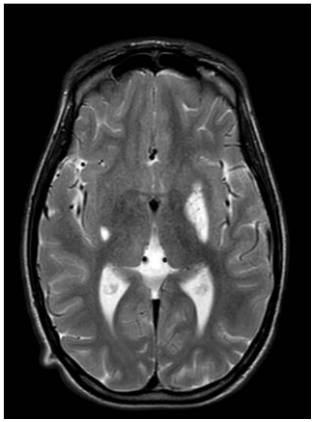


LHON

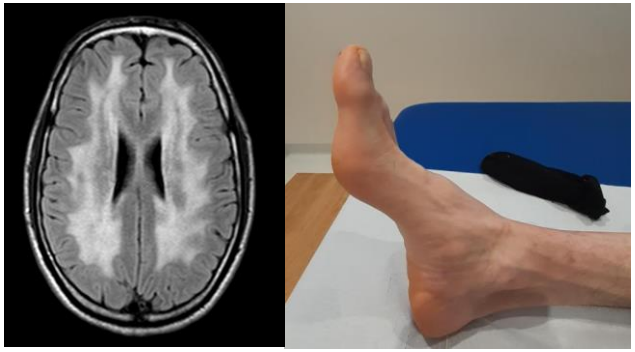


Carelli V, et al. 2019

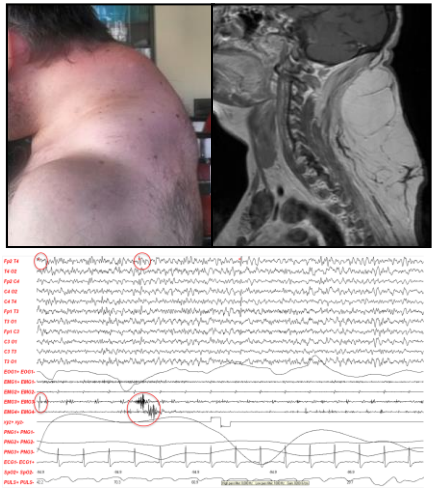
Leigh Syndrome



MNGIE



MERRF



Classical mitochondrial syndromes

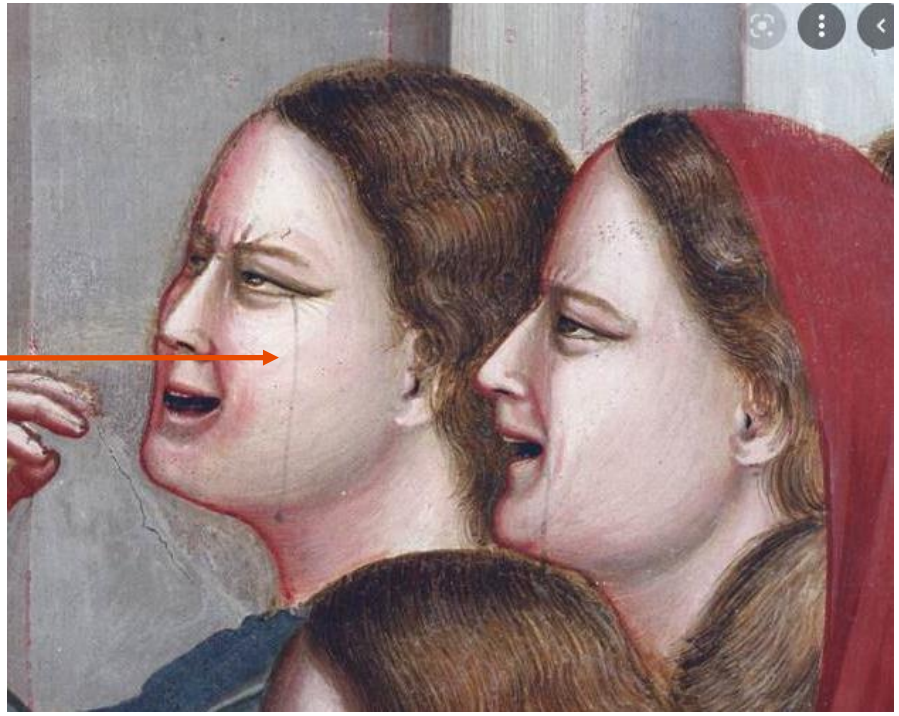
Laocoonte and His Sons, Vatican Museums

"The first time I was in Rome when I was very young, the Pope [Julius II] was told about **the discovery of some very beautiful statues in a vineyard near Santa Maria Maggiore** [on the Esquiline Hill]. The pope ordered one of his officers to run and tell **Giuliano da Sangallo** to go and see them... Since **Michelangelo Buonarroti** was always to be found at our house, my father having summoned him and having assigned him the commission of the Pope's tomb, my father wanted him to come along too... I had climbed down to where the statues were, when immediately **my father said, 'That is the Laocoon, which Pliny mentions.' Then they dug the hole wider so that that they could pull the statue out. As soon as it was visible everyone started to draw, all the while discoursing on ancient things, chatting about the ones** [ancient statues owned by the Medici] in Florence."

Letter of Francesco da Sangallo, quoted in Leonard Barkan, Unearthing the Past: Archaeology and Aestheticsin the Making of Renaissance Culture (1999)

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Refined phenotypes



The Massacre of the Innocents, Scrovegni Chapel, Padova, Italy

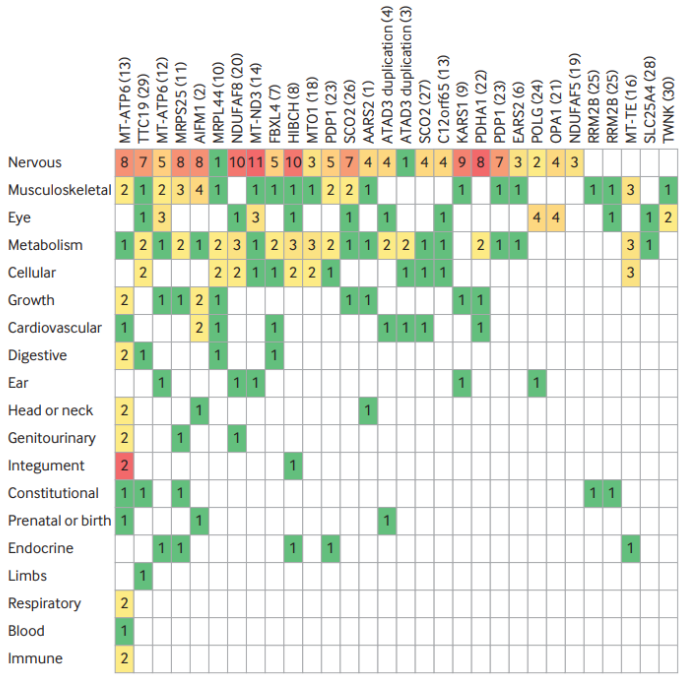
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Refined phenotypes

the bmj | BMJ 2021;375:e066288 | doi: 10.1136/bmj-2021-066288

Use of whole genome sequencing to determine genetic basis of suspected mitochondrial disorders: cohort study

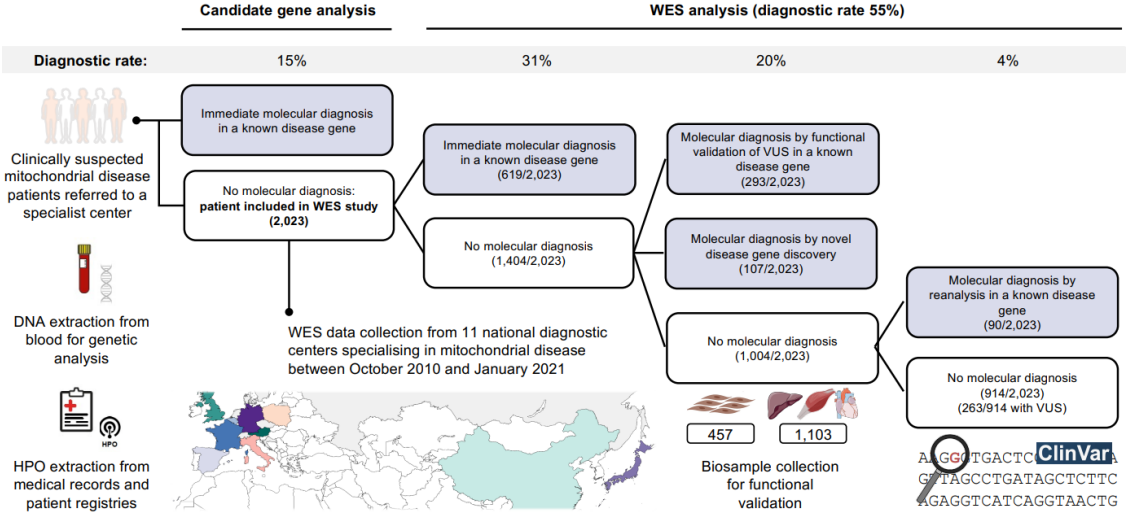
Human Phenotype Ontology (HPO) terms in patients with mitochondrial diagnoses.



Diagnosing pediatric mitochondrial disease: lessons from 2,000 exomes

Sarah L. Stenton, Masaru Shimura, Dorota Piekutowska-Abramczuk, Peter Freisinger, Felix Distelmaier, Johannes A. Mayr, Christine Makowski, Boriana Büchner, Bader Alhaddad, Charlotte L. Alston, Anna Ardissone, Rui Ban, Ivo Barić, Riccardo Berutti, Theresa Brunet, Elżbieta Ciara, Dasha Deen, Julien Gagneur, Daniele Ghezzi, Mirjana Gusic, Tobias B. Haack, Maja Hempel, Ralf A. Husain, Daniela Karall, Stefan Kölker, Urania Kotzaeridou, Thomas Klopstock, Robert Kopajtich, Vassiliki Konstantopoulou, Steffen Liez, Dominic Lenz, Albert Z. Lim, Hanna Mandel, Robert McFarland, Wolfgang Müller-Felber, Gerard Muñoz-Pujol, Akira Ohtake, Yasushi Okazaki, Rikke Olsen, Ewa Pronicka, Angela Pyle, Antonia Ribes, Dariusz Rokicki, René Santer, Manuel Schiff, Markus Schuelke, Dmitrii Smirnov, Wolfgang Sperl, Tim Strom, Frederic Tort, Polina Tsygankova, Rudy van Coster, Patrick Verloo, Jürgen-Christoph von Kleist-Retzow, Ekkehard Wilichowski, Tekla Wolstein, Manting Xu, Vicente Yépez, Michael Zech, Saskia Wortmann, Matias Wagner, Costanza Lamperti, Robert W. Taylor, Fang Fang, Agnés Rötig, Kei Murayama, Thomas Meitinger, Holger Prokisch

doi: https://doi.org/10.1101/2021.06.21.21259171



Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Refined phenotypes

Nucleic Acids Research, 2021 1
https://doi.org/10.1093/nar/gkab726

MitoPhen database: a human phenotype ontology-based approach to identify mitochondrial DNA diseases

Thiloka E. Ratnaike[1,2,3,†], Daniel Greene[4,5,†], Wei Wei[1,2], Alba Sanchis-Juan[4], Katherine R. Schon[1,2,6], Jelle van den Ameele[1,2], Lucy Raymond[6], Rita Horvath[1,2], Ernest Turro[7,‡] and Patrick F. Chinnery[1,2,*,‡]

- 89 mtDNA variants, spanning 27 genes
- 676/1352 publications
- Data from 6688 individuals in 1424 families

The MitoPhen Database 1.7

Ratnaike, Greene et al. (2021). *Nucleic Acids Research*.

MITO Phen

Download database

Select patients with variant m.8344A>G (180) Display Download

Select patients by PubMed ID 112032 (5) Display Download

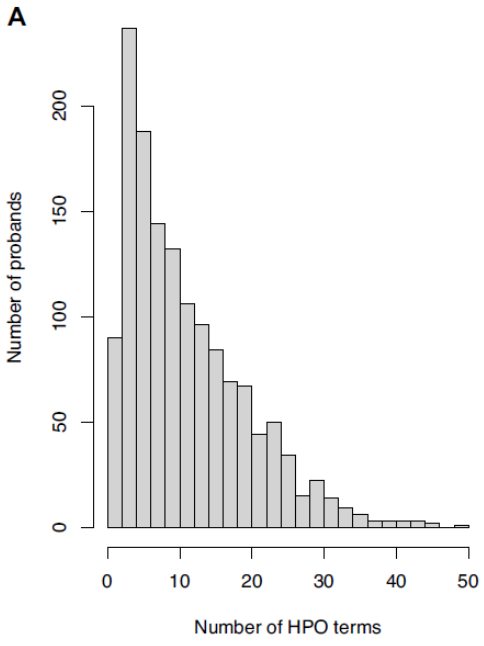
Select patients with any HPO terms:
No terms selected
Add term
Display Download

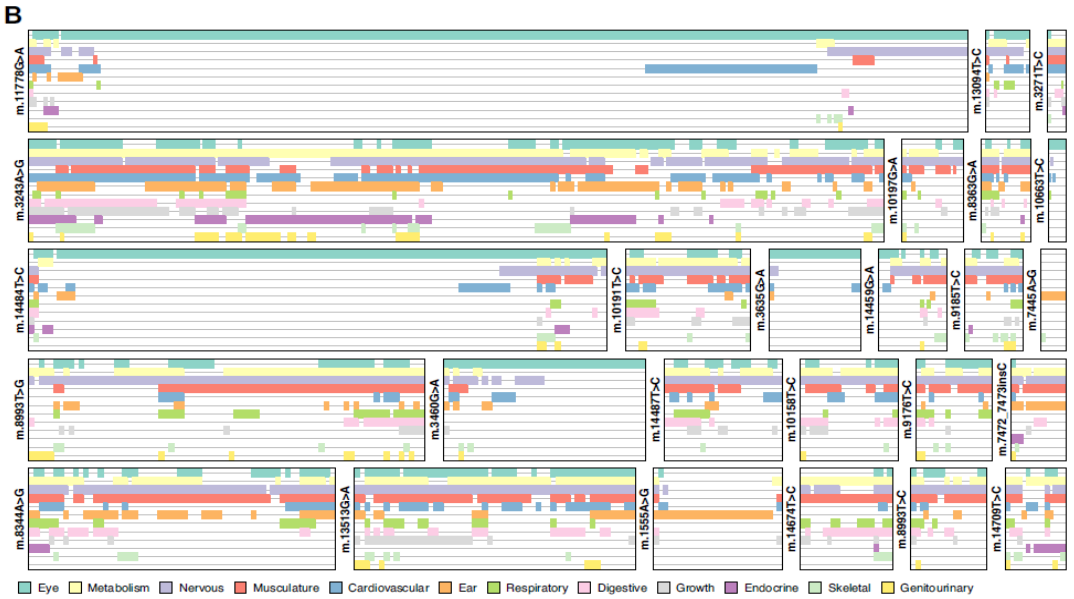
www.mitophen.org

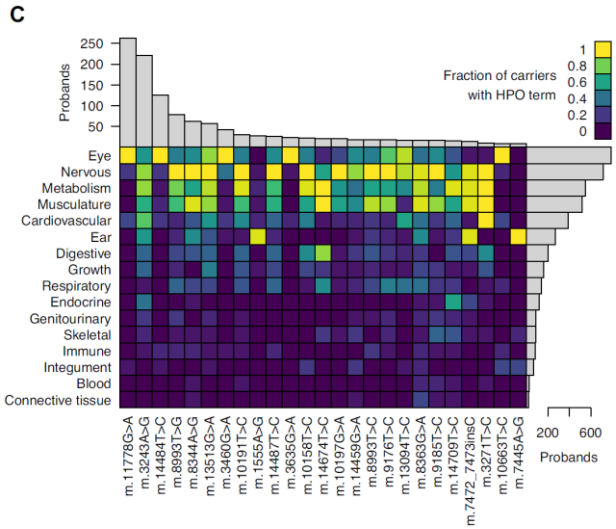
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Refined phenotypes

- The **mean number of terms** per proband was **11.4**
- **HPO terms:** nervous system, musculature, metabolism, cardiovascular, ear and eye



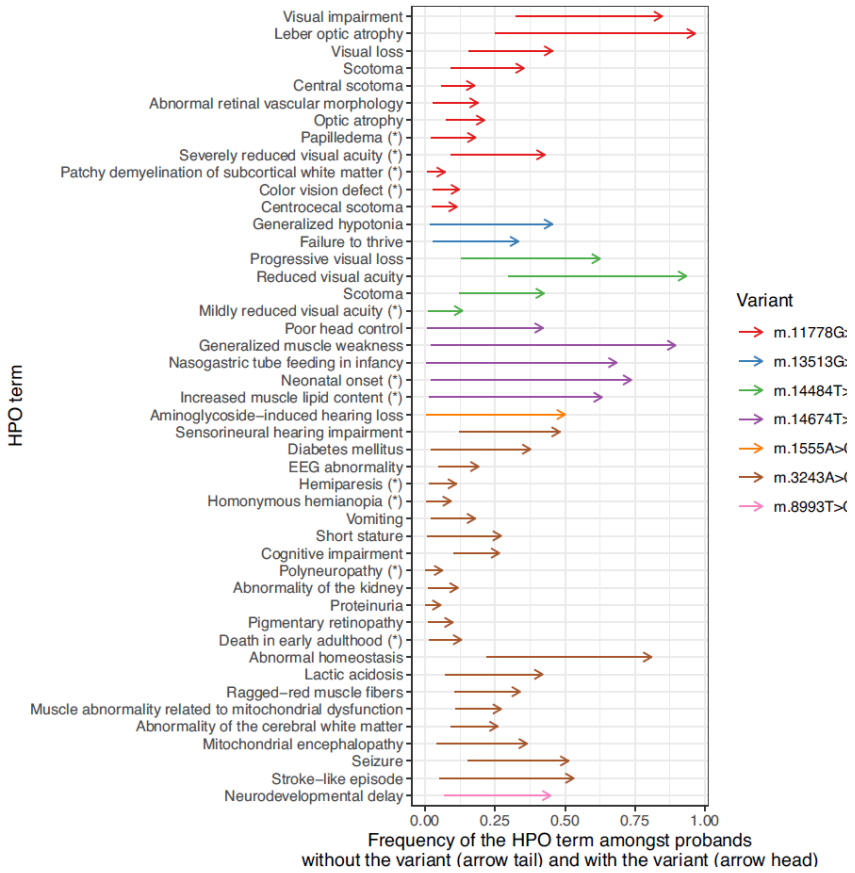


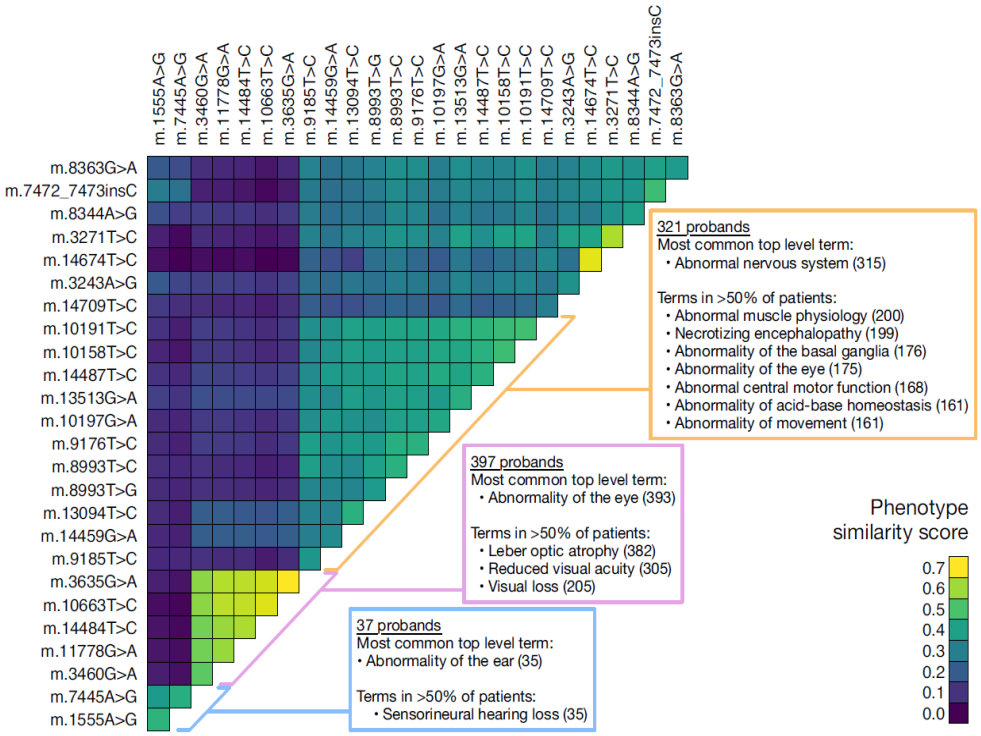


Nucleic Acids Research, 2021

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Refined phenotypes





Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

New Phenotypes

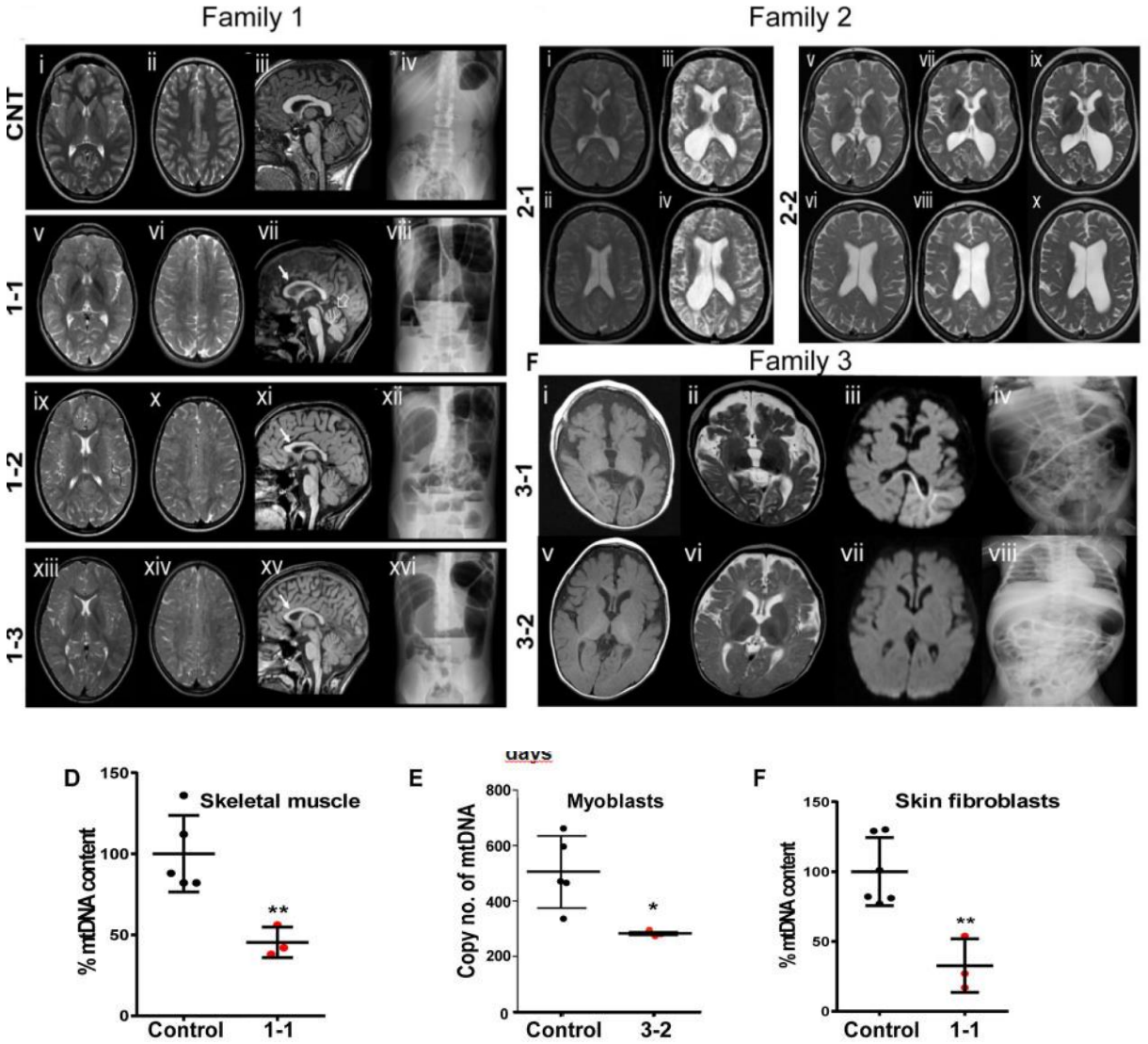
LIG3

doi:10.1093/brain/awab056 BRAIN 2021: 144; 1451–1466 | 1451

BRAIN
ORIGINAL ARTICLE

Biallelic variants in *LIG3* cause a novel mitochondrial neurogastrointestinal encephalomyopathy

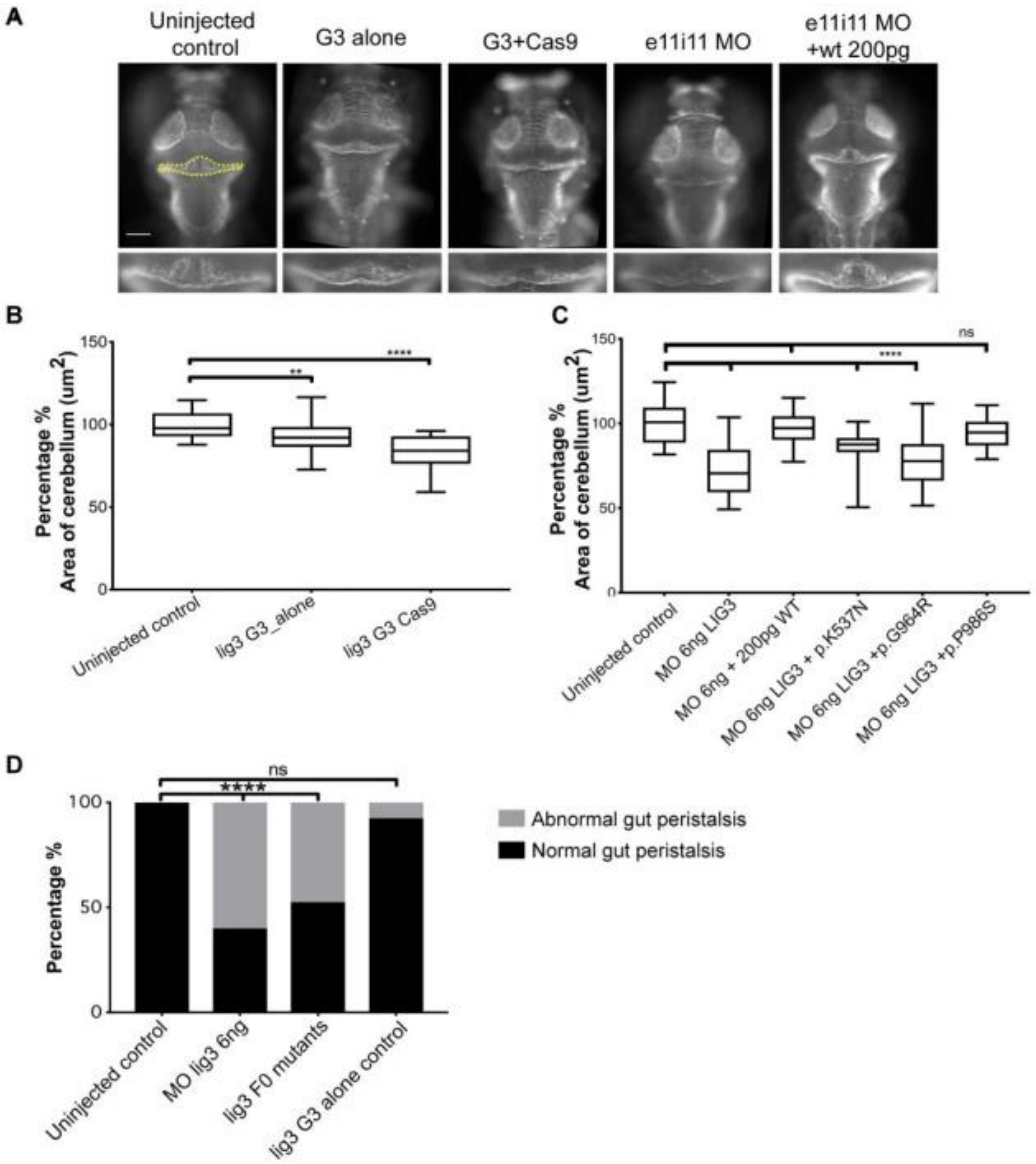
- LIG3 is the only ligase responsible for mitochondrial DNA (mtDNA) replication and maintenance
- **Seven** affected individuals
- neurogastrointestinal encephalomyopathy characterized by CIPO, neurogenic bladder, myopathic changes, and neurological impairment with stroke-like episodes, epilepsy and leukoencephalopathy



Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

New Phenotypes

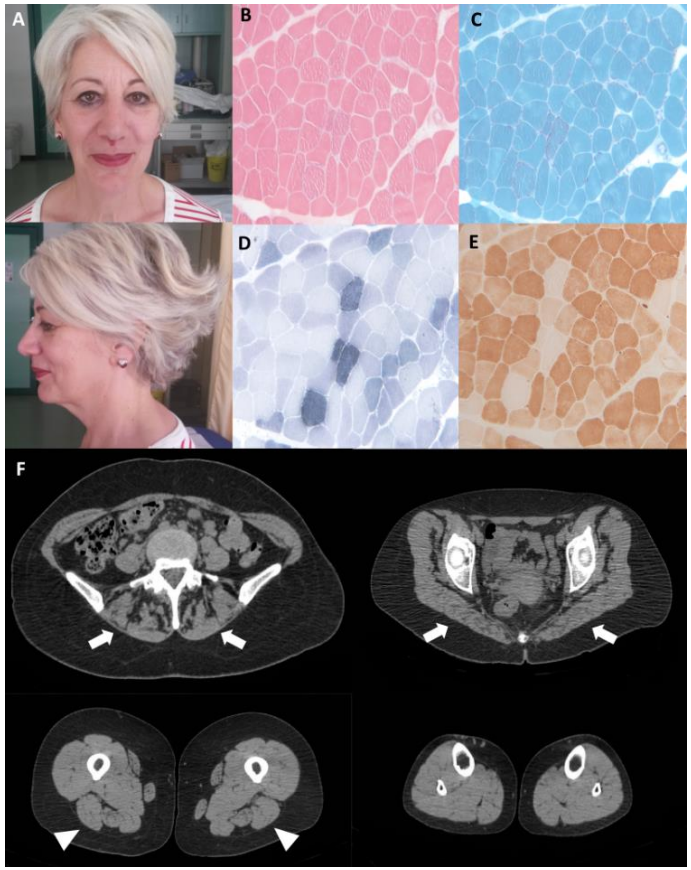
LIG3

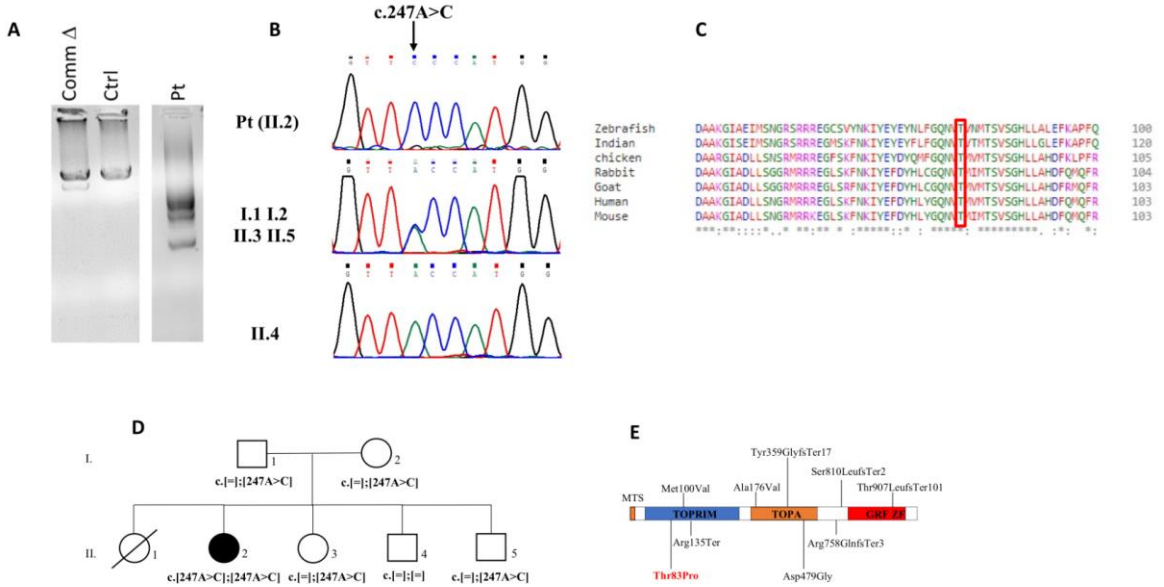


Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

New Phenotypes
TOP3A

Rosalba Carrozzo
Alessandra Torraco
Daniela Verrigni
Enrico Bertini



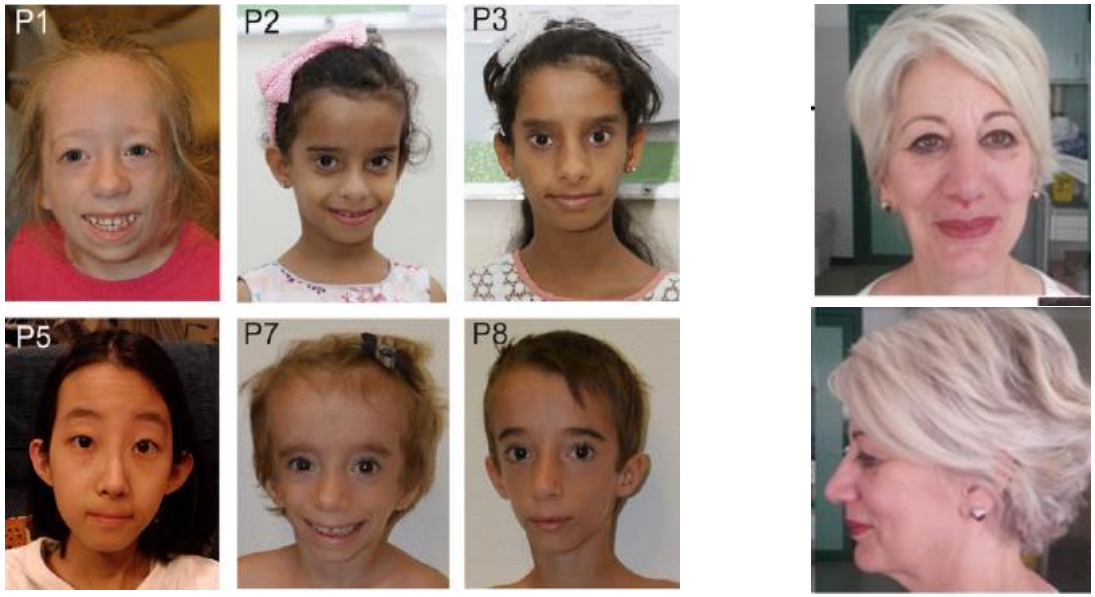


Primiano G., et al. Neurology:Genetics 2022

New Phenotypes
TOP3A

The American Journal of Human Genetics *103*, 221–231, August 2, 2018 **ARTICLE**

Mutations in *TOP3A* Cause a Bloom Syndrome-like Disorder



Bloom syndrome-like disorder

PMM/PEO Plus

mtDNA depletion ⟷ **Multiple mtDNA deletions**

- **Similarities**: short stature, dilated cardiomyopathy, narrow face with prominent nose for paucity of subcutaneous fat, absence of malignancies
- **Differences**: a late onset of disease, no cafe´-au-lait macules

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Expanding phenotypes

Movement disorders

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

ORIGINAL COMMUNICATION

Check for updates

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]

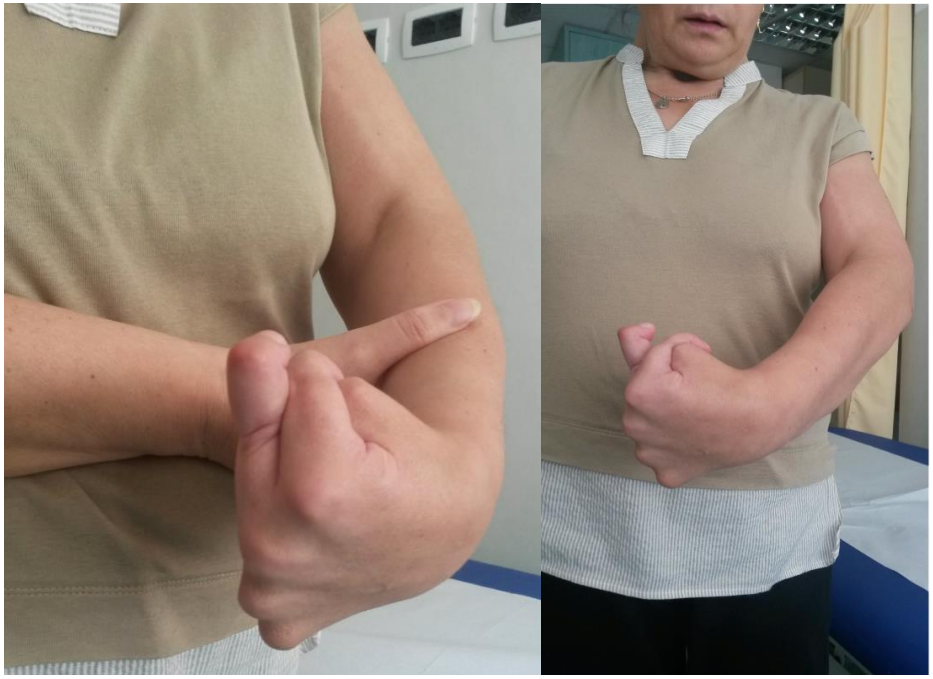
Journal of *Clinical Medicine*

MDPI

Article

Movement Disorders in Children with a Mitochondrial Disease: A Cross-Sectional Survey from the Nationwide Italian Collaborative Network of Mitochondrial Diseases

Chiara Ticci [1], Daniele Orsucci [2], Anna Ardissone [3], Luca Bello [4], Enrico Bertini [5], Irene Bonato [6], Claudio Bruno [6], Valerio Carelli [7,8], Daria Diodato [5], Stefano Doccini [1], Maria Alice Donati [9], Claudia Dosi [1], Massimiliano Filosto [10], Chiara Fiorillo [11], Chiara La Morgia [7,12], Costanza Lamperti [13], Silvia Marchet [13], Diego Martinelli [5], Carlo Minetti [11], Maurizio Moggio [14], Tiziana Enrica Mongini [15], Vincenzo Montano [16], Isabella Moroni [3], Olimpia Musumeci [17], Elia Pancheri [18], Elena Pegoraro [4], Guido Primiano [19,20], Elena Procopio [9], Anna Rubegni [1], Roberta Scalise [1,21], Monica Sciacco [14], Serenella Servidei [19,20], Gabriele Siciliano [16], Costanza Simoncini [16], Deborah Tolomeo [1], Paola Tonin [18], Antonio Toscano [17], Flavia Tubili [9], Michelangelo Mancuso [16], Roberta Battini [1,16,*] and Filippo Maria Santorelli [1]



***POLG* c.428C>T [Ala143Val], 2956T>G [Tyr986Asp]**

Gemelli

Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

Expanding phenotypes

Spinal cord involvement

life

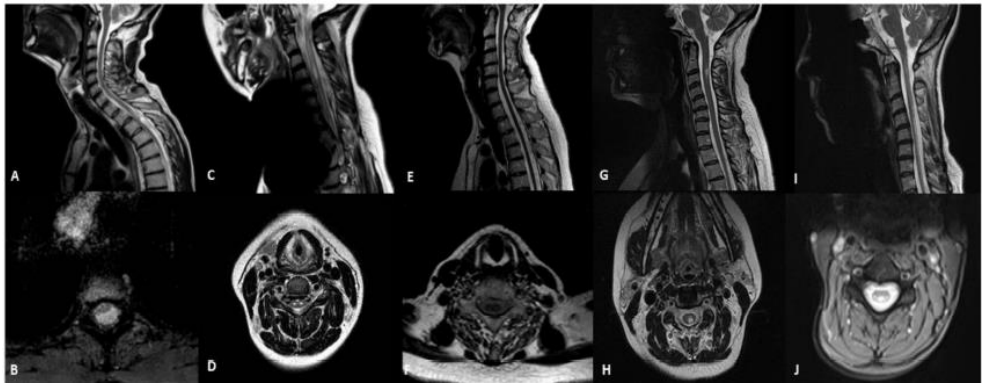
MDPI

Communication

Spinal Cord Involvement in Adult Mitochondrial Diseases: A Cohort Study

Guido Primiano [1,2,*], Paolo Mariotti [1], Ida Turrini [1], Cristina Sancricca [1], Andrea Sabino [2], Alessandra Torraco [3], Rosalba Carrozzo [3] and Serenella Servidei [1,2]

- **9,8%, 5/51 patients**



Neurological Sciences (2022) 43:2081–2084
https://doi.org/10.1007/s10072-022-05881-8

BRIEF COMMUNICATION

Kearns-Sayre syndrome: expanding spectrum of a "novel" mitochondrial leukomyeloencephalopathy

Marco Moscatelli[1] · Anna Ardissone[2] · Eleonora Lamantea[3] · Giovanna Zorzi[2] · Claudio Bruno[4] · Isabella Moroni[2] · Alessandra Erbetta[1] · Luisa Chiapparini[1]

Neuroradiology (2020) 62:1315–1321
https://doi.org/10.1007/s00234-020-02501-0

PAEDIATRIC NEURORADIOLOGY

Spinal cord involvement in Kearns-Sayre syndrome: a neuroimaging study

Pasquini Luca[1,2] · Guarnera Alessia[1,2] · Rossi-Espagnet Maria Camilla[1,2] · Napolitano Antonio[3] · Martinelli Diego[4] · Deodato Federica[4] · Diodato Daria[5] · Carrozzo Rosalba[5] · Dionisi-Vici Carlo[4] · Longo Daniela[1]

- **54.5%, 6/11**

AJNR Am J Neuroradiol 42:389–96 Feb 2021

Involvement of the Spinal Cord in Primary Mitochondrial Disorders: A Neuroimaging Mimicker of Inflammation and Ischemia in Children

C.A.P.F. Alves, A. Goldstein, S.R. Teixeira, J.S. Martin-Saavedra, I.P. de Barcelos, G. Fadda, L. Caschera, M. Kidd, F.G. Gonçalves, E.M. McCormick, M.J. Falk, Z. Zolkipli-Cunningham, A. Vossough, and G. Zuccoli

- **58%, 19/33**

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Emerging clinical aspects

ARTICLE

Sleep-Disordered Breathing in Adult Patients With Mitochondrial Diseases

A Cohort Study

Guido Primiano, MD, Valerio Brunetti, MD, Catello Vollono, MD, PhD, Anna Losurdo, MD, Rossana Moroni, PhD, Giacomo Della Marca, MD, and Serenella Servidei, MD

Correspondence
Dr. Primiano
guido.primiano@gmail.com

Neurology® 2021;96:e241-e249. doi:10.1212/WNL.0000000000011005

Figure 1 Distribution of the SDB in Mitochondrial Diseases

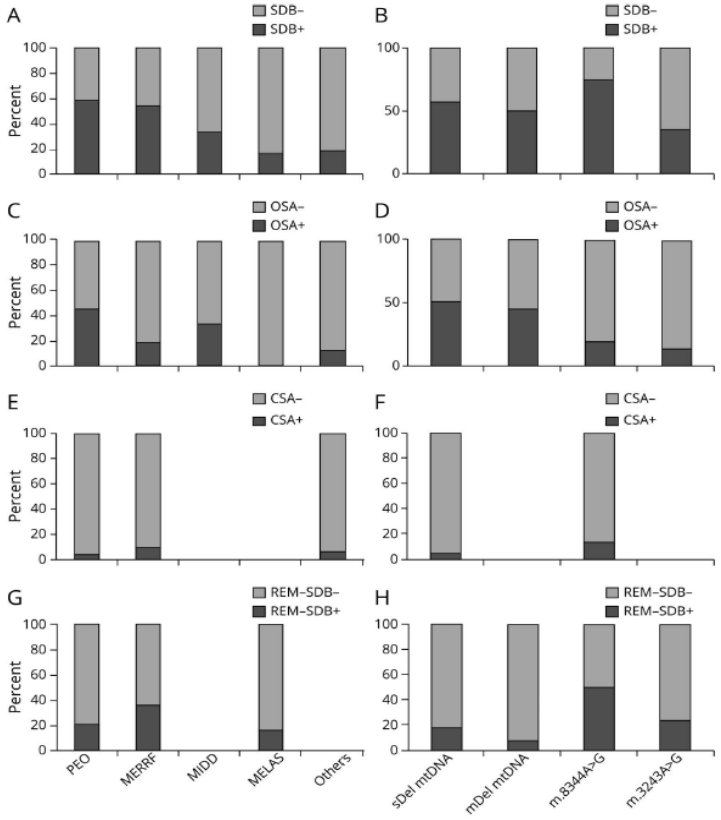
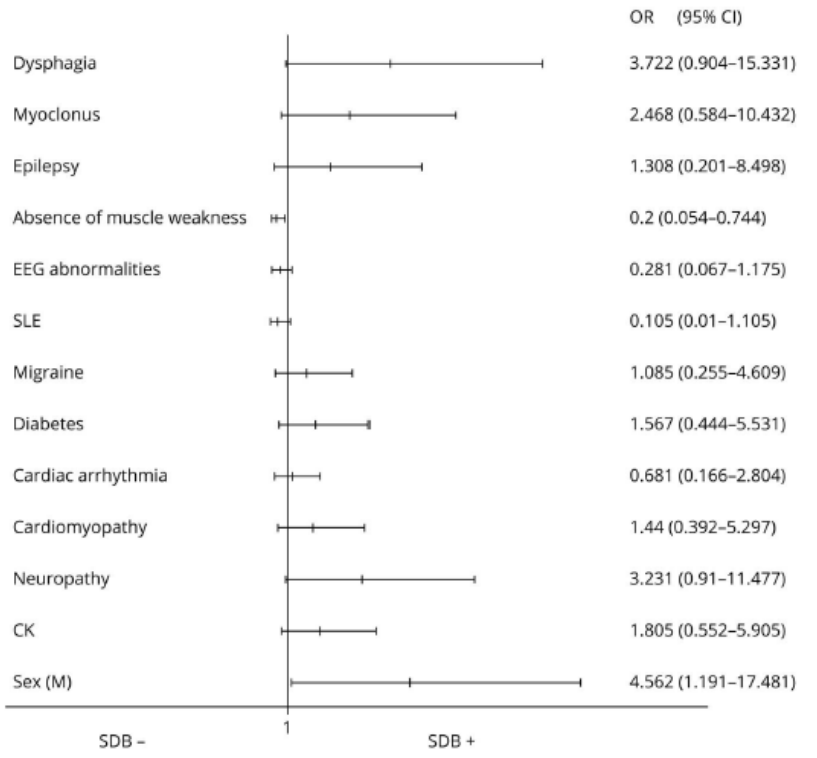


Figure 2 Association Between SDB and Clinical Variables



Gemelli

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Emerging clinical aspects

NATURE REVIEWS | ENDOCRINOLOGY VOLUME 13 | FEBRUARY 2017

Mitochondrial disease and endocrine dysfunction

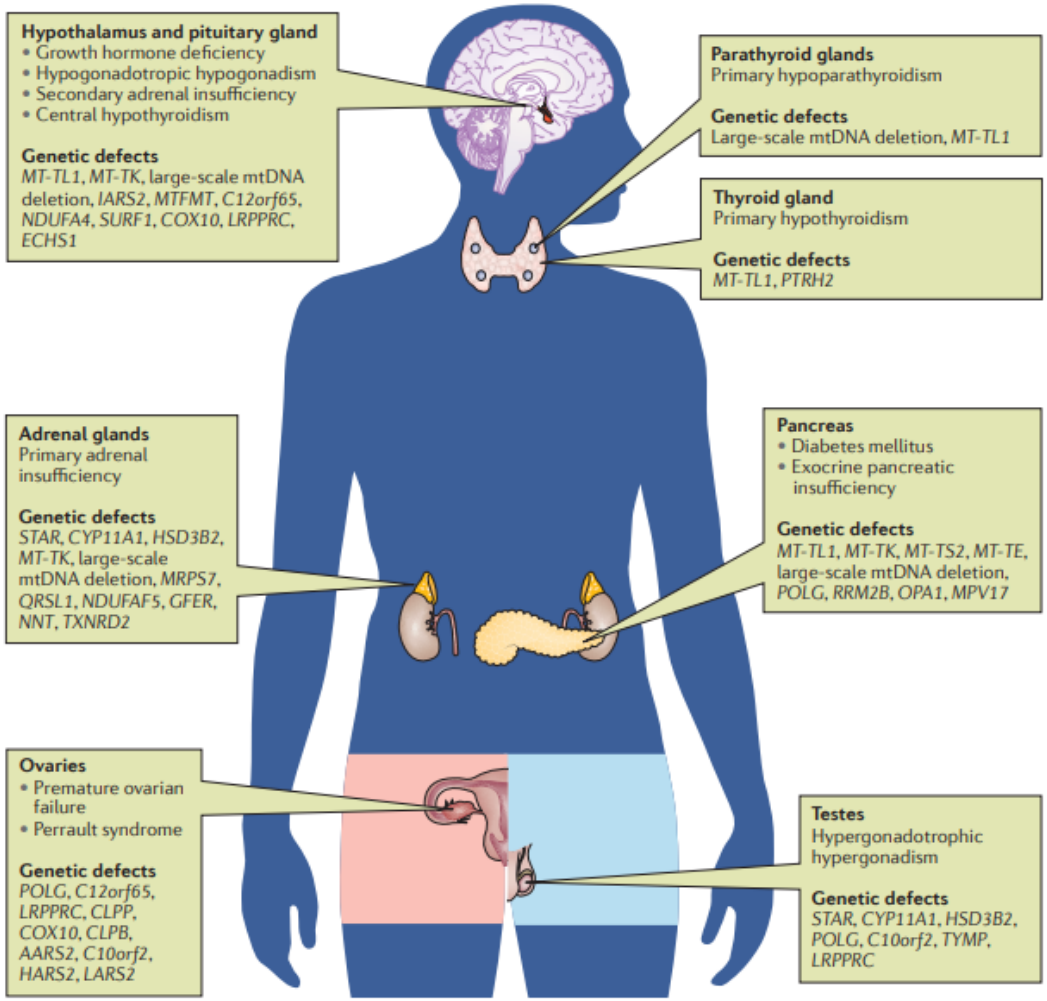
Jasmine Chow[1], Joyeeta Rahman[2], John C. Achermann[2], Mehul T. Dattani[2,3] and Shamima Rahman[2,4]

ENDOCRINE SOCIETY

Mitochondrial Dysfunction in Primary Ovarian Insufficiency

Dov Tiosano, Jason A. Mears, and David A. Buchner

Endocrinology
Endocrine Society



Gemelli

Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

Emerging clinical aspects

ORIGINAL ARTICLE

Safety of drug use in patients with a primary mitochondrial disease: An international Delphi-based consensus

Maaike C. De Vries[1] | David A. Brown[2] | Mitchell E. Allen[2] | Laurence Bindoff[3,4] | Gráinne S. Gorman[5,6] | Amel Karaa[7] | Nandaki Keshavan[8,9] | Costanza Lamperti[10] | Robert McFarland[5,6] | Yi Shiau Ng[5,6] | Mar O'Callaghan[11,12] | Robert D. S. Pitceathly[13] | Shamima Rahman[8,9] | Frans G. M. Russel[14] | Kristin N. Varhaug[3,4] | Tom J. J. Schirris[14] | Michelangelo Mancuso[15]

TABLE 2 Points of attention regarding drug prescription in patients with a mitochondrial disease (detailed description in Section 4)

Specific drug/drug group/clinical condition/genotype	Points of attention
Specific drug/drug group/genotype	
Aminoglycosides	The mitochondrial 12S rRNA is a hot spot for mutations associated with both aminoglycoside-induced and non-syndromic hearing loss. Screening for these mtDNA mutations is strongly recommended before elective long-term treatment is planned. The benefits of the drug in emergency treatment, as a very effective broad-spectrum antibiotic, outweigh the risks in these situations.
Valproic acid	Should be used only in exceptional circumstances. The drug is absolutely contraindicated in patients with mitochondrial disease due to *POLG* mutations. Valproic acid should not be used in patients with known liver disease and/or clinical signs suspicious for *POLG* disease.
Neuromuscular blocking agents	Extra caution and monitoring should be performed for patients manifesting a predominantly myopathic phenotype.
Specific clinical condition	
General anaesthesia and surgery	Catabolism should be prevented by minimising preoperative fasting and administering intravenous glucose perioperatively during prolonged anaesthesia, unless the patient is on a ketogenic diet.
Duration of treatment	The duration of drug administration may play a role in whether or not side effects develop. Duration of treatment should be guided by individual patient needs and their response to specific treatments.
Renal impairment	Many patients with a mitochondrial disease have renal impairment; drug dose adjustment should be considered particularly when active drug moieties are renally cleared.
Metabolic acidosis (lactic acidosis)	Metabolic acidosis (lactic acidosis) may occur in patients with mitochondrial disease, therefore drugs that can cause acidosis should be prescribed with caution. Regular clinical review and monitoring of acid-base status in blood is recommended.

JIMD SSIEM WILEY

LETTER TO THE EDITOR

JIMD SSIEM

A severe linezolid-induced rhabdomyolysis and lactic acidosis in Leigh syndrome

Guido Primiano[1]
Serenella Servidei[1,2]

Gemelli

Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

Emerging clinical aspects

Mitochondrion 58 (2021) 243–245

SARS-CoV-2 infection in patients with primary mitochondrial diseases: Features and outcomes in Italy

Michelangelo Mancuso[a,*], Chiara La Morgia[b], Maria Lucia Valentino[b,c], Anna Ardissone[d], Costanza Lamperti[e], Elena Procopio[f], Caterina Garone[g,h], Gabriele Siciliano[a], Olimpia Musumeci[i], Antonio Toscano[i], Guido Primiano[j,k], Serenella Servidei[j,k], Valerio Carelli[b,c]

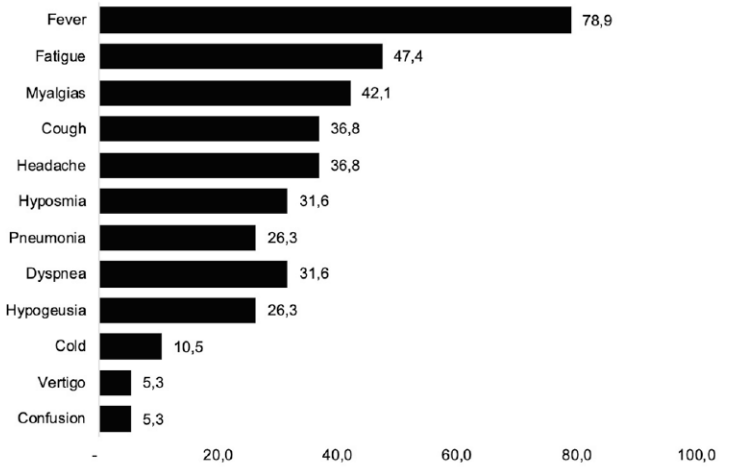


Fig. 1. Percentage of COVID-19-related symptoms in the 27 symptomatic mitochondrial patients.

CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

COVID-19–Related Outcomes in Primary Mitochondrial Diseases

An International Study

Chiara Pizzamiglio, MD,* Pedro M. Machado, MD, PhD,* Rhys H. Thomas, MD, PhD, Gráinne S. Gorman, MD, PhD, Robert McFarland, MD, PhD, Michael G. Hanna, MD, FRCP, and Robert D. S. Pitceathly, MD, PhD, on behalf of the MitoCOVID-19 Study Group

Neurology® 2022;98:576-582. doi:10.1212/WNL.0000000000200240

- **Seventy-nine PMDs** from 10 countries (mean age 41.5 ± 18 years);
- 25 (**32%**) were **hospitalized**, 48 (61%) recovered fully, 28 (35%) improved with sequelae, and 3 (**4%**) **died**;
- Statistically significant differences in **hospitalization status** were observed in baseline status, including the **NMDAS score** ($p = 0.003$) and mRS ($p = 0.001$), presence of **respiratory dysfunction** ($p < 0.001$), **neurologic involvement** ($p = 0.003$), and **more than 4 comorbidities** ($p = 0.002$).
- **Respiratory dysfunction** is an independent risk factor for severe COVID-19 in PMDs while high **disease burden and coexisting comorbidities contribute toward COVID-19–related hospitalization.**

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Neuropathological investigations

BRAIN COMMUNICATIONS 2022: Page 2 of 16

Neurodegenerative and functional signatures of the cerebellar cortex in m.3243A > G patients

Roy A. M. Haast,[1] Irenaeus F. M. De Coo,[2] Dimo Ivanov,[3] Ali R. Khan,[1,4,5] Jacobus F. A. Jansen,[6,7,8] Hubert J. M. Smeets[2,8] and Kâmil Uludağ[9,10,11]

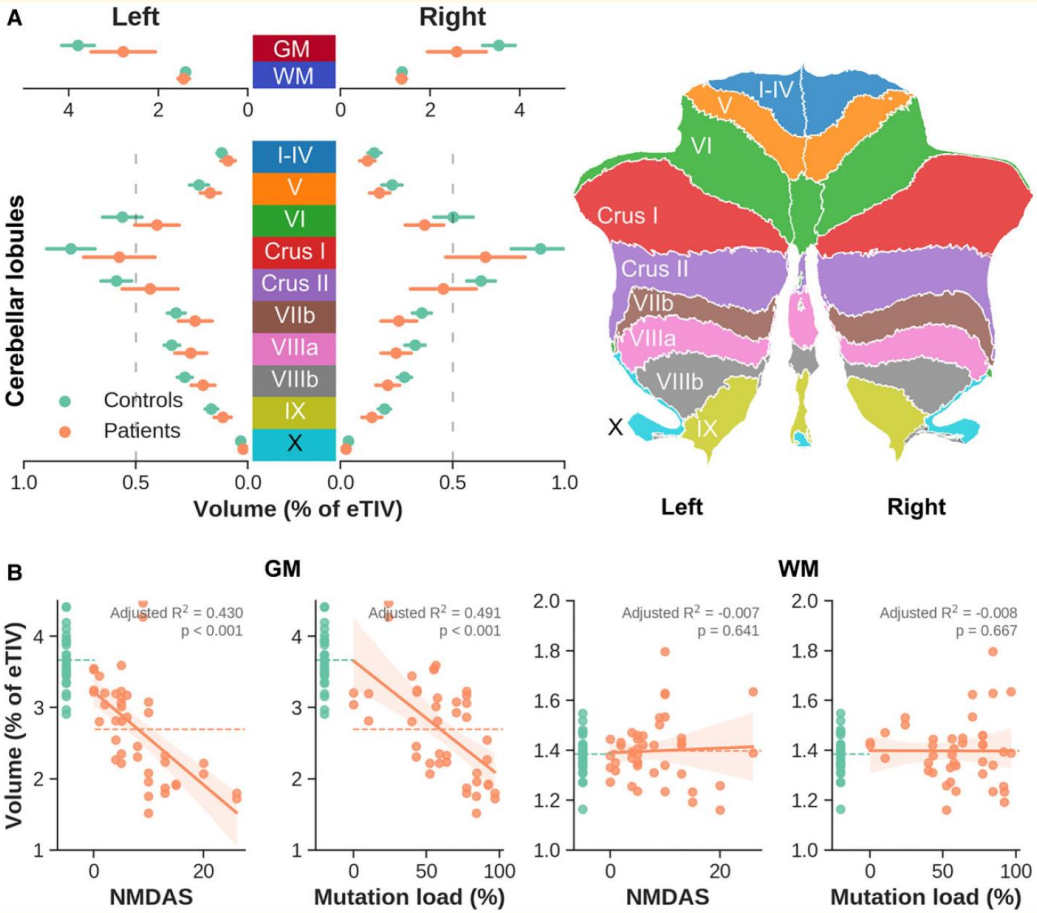


Figure 2 Cerebellar GM and WM volumes. (**A**) Comparison of volume (presented as % of eTIV|on the *x*-axis) between controls (green) and m.3243A > G patients (orange) for left and right hemisphere GM and WM (*top*), as well as per cerebellar lobule GM (*bottom*), colour-coded based on the right panel legend. (**B**) First two columns: correlation between GM volume (*y*-axis) and NMDAS or corrected UEC mutation load (*x*-axes). Last two columns: similar to first two columns but using WM volume (*y*-axis). Shaded areas show 95% confidence intervals.

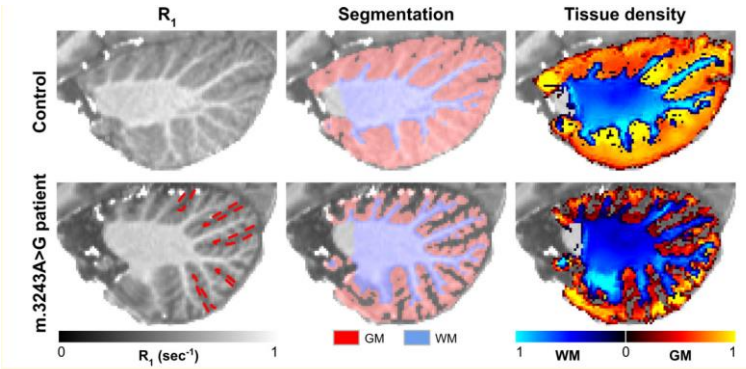


Figure 1 Example data. Left to right: R_1, GM (red) and WM (blue) segmentation masks and corresponding tissue density maps are shown for a control (*top* row) and m.3243A > G patient (*bottom* row). Dashed red lines indicate the inter-folial spacing for the patient.

Gemelli

Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

Mitochondrial diseases

Mitochondrial Diseases

Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

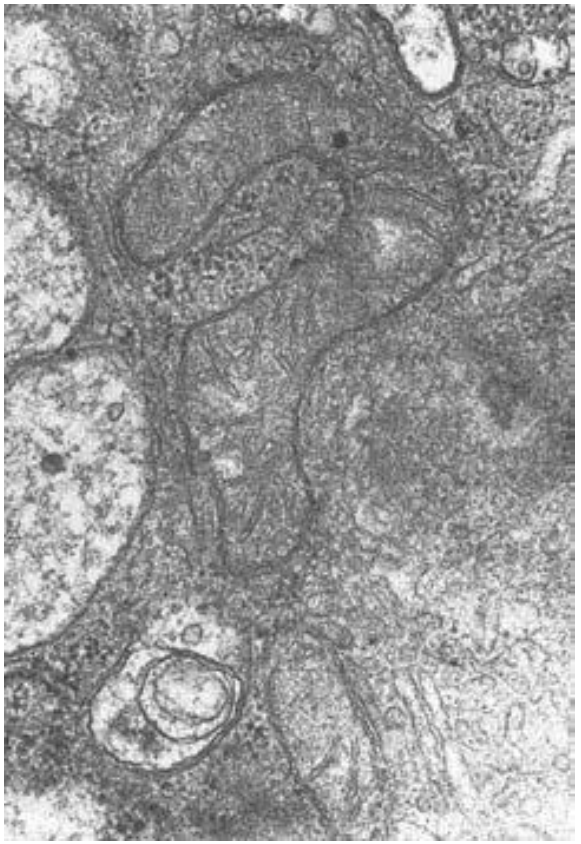
Medicina mitocondriale

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Serenella Servidei
Cristina Sancricca
Andrea Sabino
Manuela Papacci

Bambino Gesù
Ospedale Pediatrico

Enrico Bertini
Rosalba Carrozzo
Alessandra Torraco
Daniela Verrigni



Italian Network of Mitochondrial Diseases

Mitocon
Insieme per lo studio e la cura delle malattie mitocondriali

- **guidoalessandro.primiano@policlinicogemelli.it**