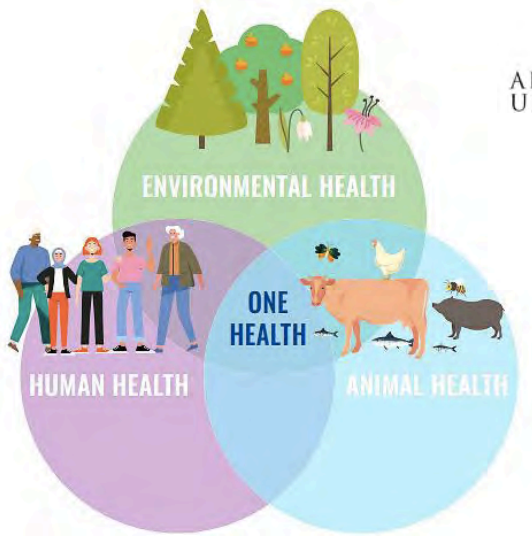

ALMA MATER STUDIORUM
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CENTRO INTERDIPARTIMENTALE ALMA MATER INSTITUTE ON HEALTHY PLANET - ALMA HEALTHY PLANET

Dai mitocondri al microbioma, quanti genomi regolano la nostra interazione con l'ambiente?

Valerio Carelli, MD, PhD

Dipartimento di Scienze Biomediche e Neuromotorie (DIBINEM), Universita' di Bologna

Direttore del Programma di Neurogenetica
IRCCS Istituto di Scienze Neurologiche di Bologna, Bellaria Hospital

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

isnb IRCCS Istituto delle Scienze Neurologiche di Bologna

«Genetics loads the gun, but environment pulls the trigger»…the EXPOSOME paradigm

European Commission

Topic addressed: SC1-BHC-28-2019

Title: EXploiting TRIgenomics in a Multiexposome study - EXTRIM

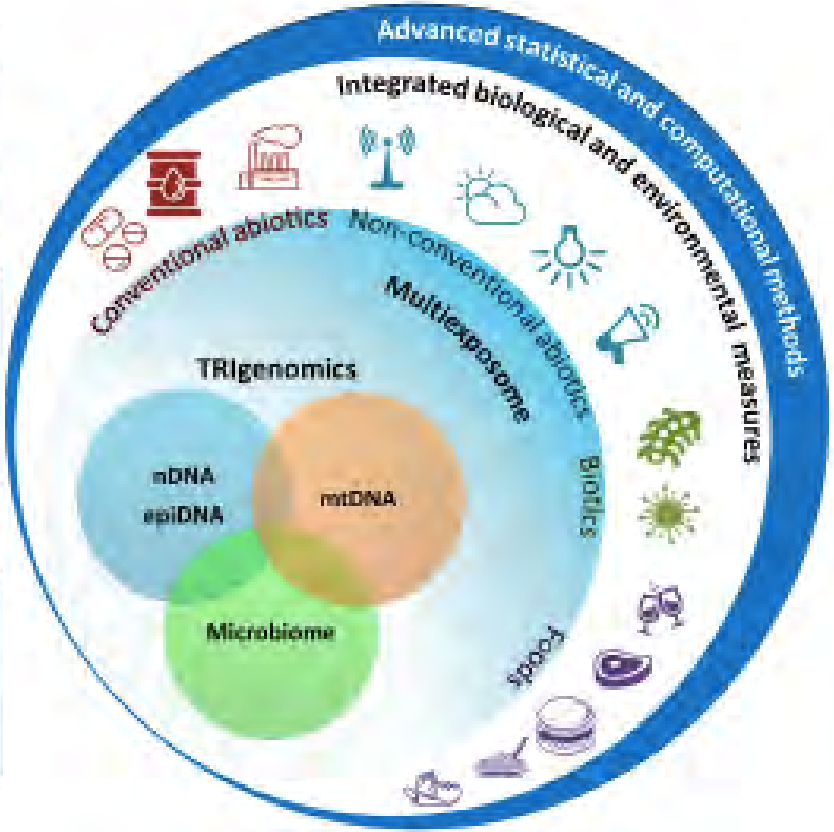
To fill these gaps and as new starting point, EXTRIM consortium envisages that the high complexity of **GxE interaction needs to be holistically viewed in a larger framework** capturing the "***totality of environmental exposures***", but also all genomic components whose combined inherited variability, and somatic environment-driven remodeling impinges on all aspects of human life [3]. EXTRIM will tackle this challenge first by defining a new landscape for the "***totality of genomes***", which besides the "static" inherited genetic variation will take into account also the more "dynamic" genomic adaptive changes to environmental exposures.

This redefined "***TRIgenomics***" individual genetic layout will therefore include:

a) the ***nuclear genome*** **(nDNA) sequence**, which by epigenetic regulation may react to environment (**epiDNA**);
b) the ***mitochondrial genome*** **(mtDNA) sequence** of ancestral bacterial origin, interacting with the nuclear genome by fast turnover of variants and changing copy number, making it the best adaptive genome;
c) the metagenome of bacterial populations (microbiota) living on our body, known as ***microbiome***.

EXTRIM will also redefine the framework of environmental exposures at the basis of multifactorial pathogenesis of NCDs, by identifying a broadened landscape of many different "Exposomes" as "***Multiexposome***".

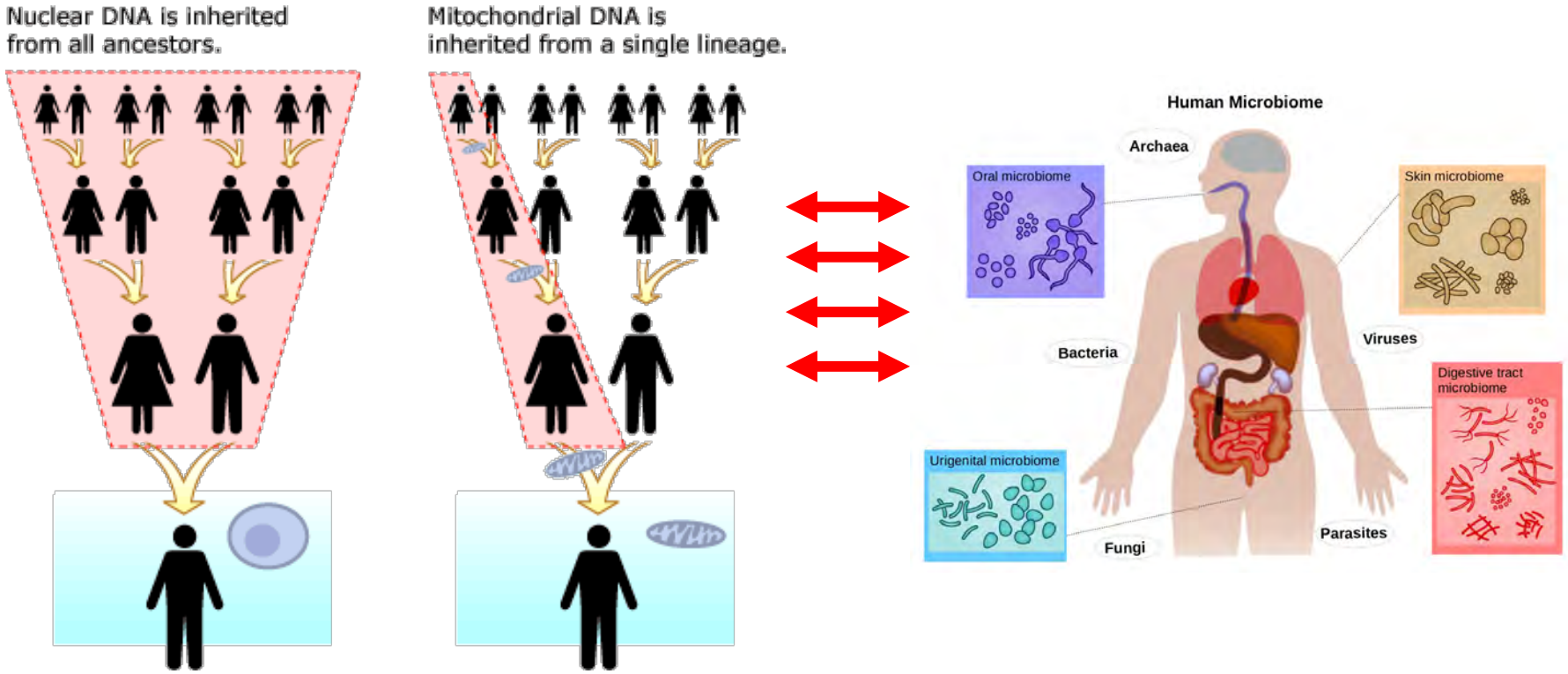
"***Multiexposome***" will be accomplished by adding to the well-recognized combination of **biotics** (fungi, bacteria, virus, etc.) and **abiotics** (pollutants and chemicals, including therapeutic drugs and pharmaceuticals) **in soil, water, and air** [4], also less-conventional factors such as **electromagnetic waves** [5,6], **noise** [7], **foods** [8] and, particularly, **climate change**, affecting the social and environmental determinants of health [9], and the neglected **artificial light pollution at night**, to which humans and the whole biosphere are now massively exposed [10-12].



Review Article

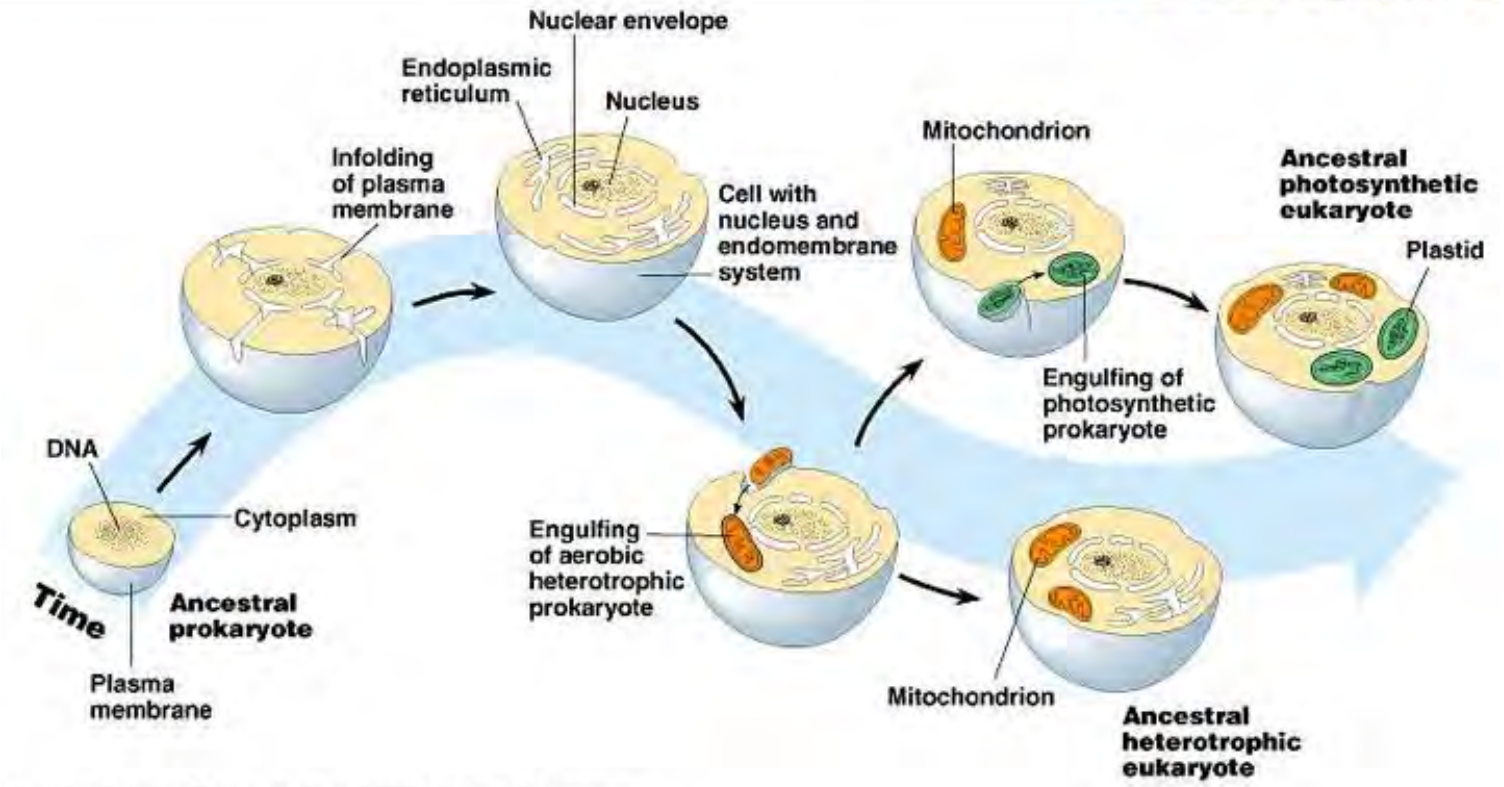
The Three Genetics (Nuclear DNA, Mitochondrial DNA, and Gut Microbiome) of Longevity in Humans Considered as Metaorganisms

Paolo Garagnani,[1,2,3] Chiara Pirazzini,[1,2] Cristina Giuliani,[4] Marco Candela,[5] Patrizia Brigidi,[5] Federica Sevini,[1,2] Donata Luiselli,[4] Maria Giulia Bacalini,[1,2] Stefano Salvioli,[1,2] Miriam Capri,[1,2] Daniela Monti,[6] Daniela Mari,[7,8] Sebastiano Collino,[9] Massimo Delledonne,[10] Patrick Descombes,[11] and Claudio Franceschi[1,2,12,13]



Mitochondria derive from bacteria: are they our intracellular microbiome?

Lynn Margulis (1938-2011)
Endosymbiotic origin of mitochondria (1967)



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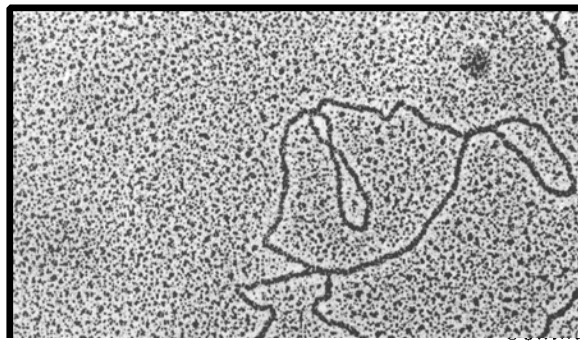
Mitochondria contain their own genome: mtDNA (16569 bp long)

Margit Nass



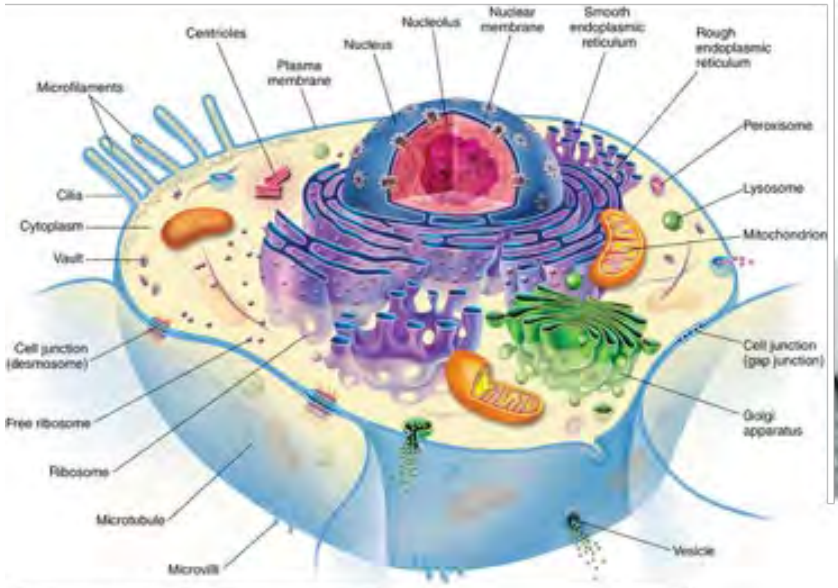
INTRAMITOCHONDRIAL FIBERS

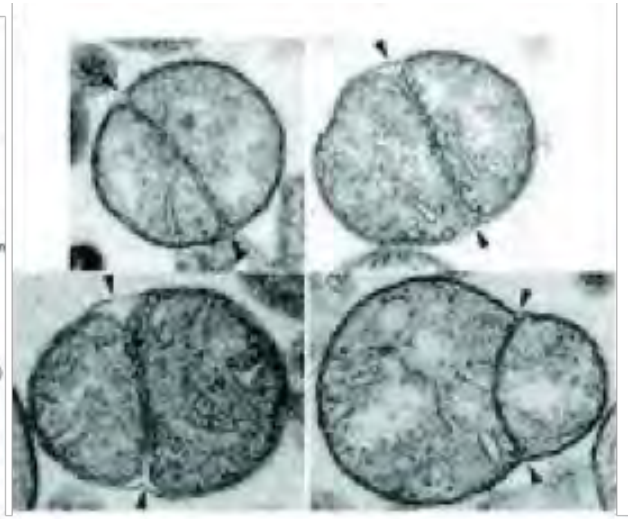
INTRAMITOCHONDRIAL FIBERS WITH DNA CHARACTERISTICS

Studies of the last few years have demonstrated that a small amount of DNA is located specifically in one or more central regions of mitochondria[1–4] representing cell types of all vertebrate and invertebrate phyla.[4] A DNA differing in compositional[5–12] and metabolic[6, 8, 9] properties from nuclear DNA can be isolated from purified mitochondria of many organisms. A rapidly expanding body of literature, already too voluminous to cite fully in publications other than a review, deals with mitochondrial DNA, RNA, protein synthesis, mitochondrial "self-duplication," and genetic determinants (cf. refs. 4 and 13).

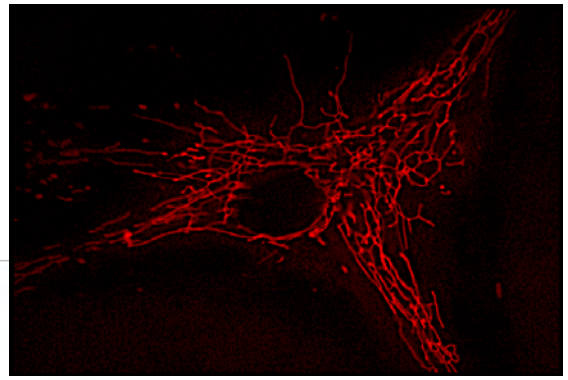
Pertinent to the present paper are the observations that mitochondrial and nuclear DNA may not merely differ in guanine plus cytosine content (a difference which may be small[9, 12] or undetectable in some mammalian species[10]) but also in their renaturation properties. Heat- or alkali-denatured DNA's of mitochondria from various mammalian cell types[10–12] and yeast[10] renature under conditions in which

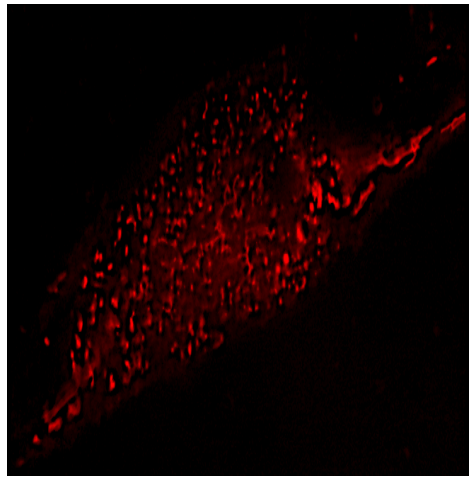
Mitochondria are highly dynamic



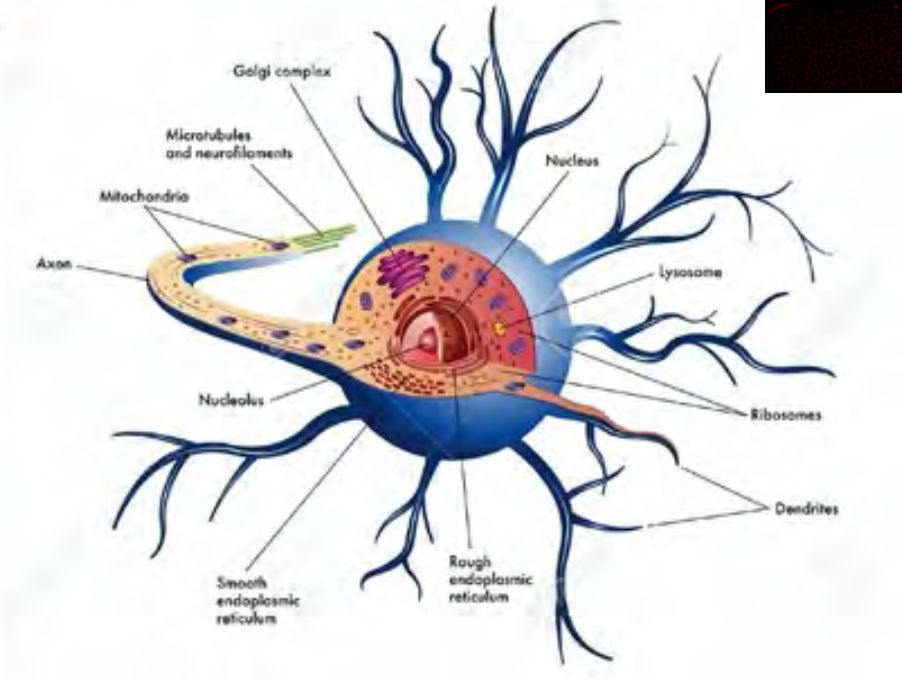


Mito-Fusion





Mito-Fission



Mitochondria at the crossroad of many metabolic pathways

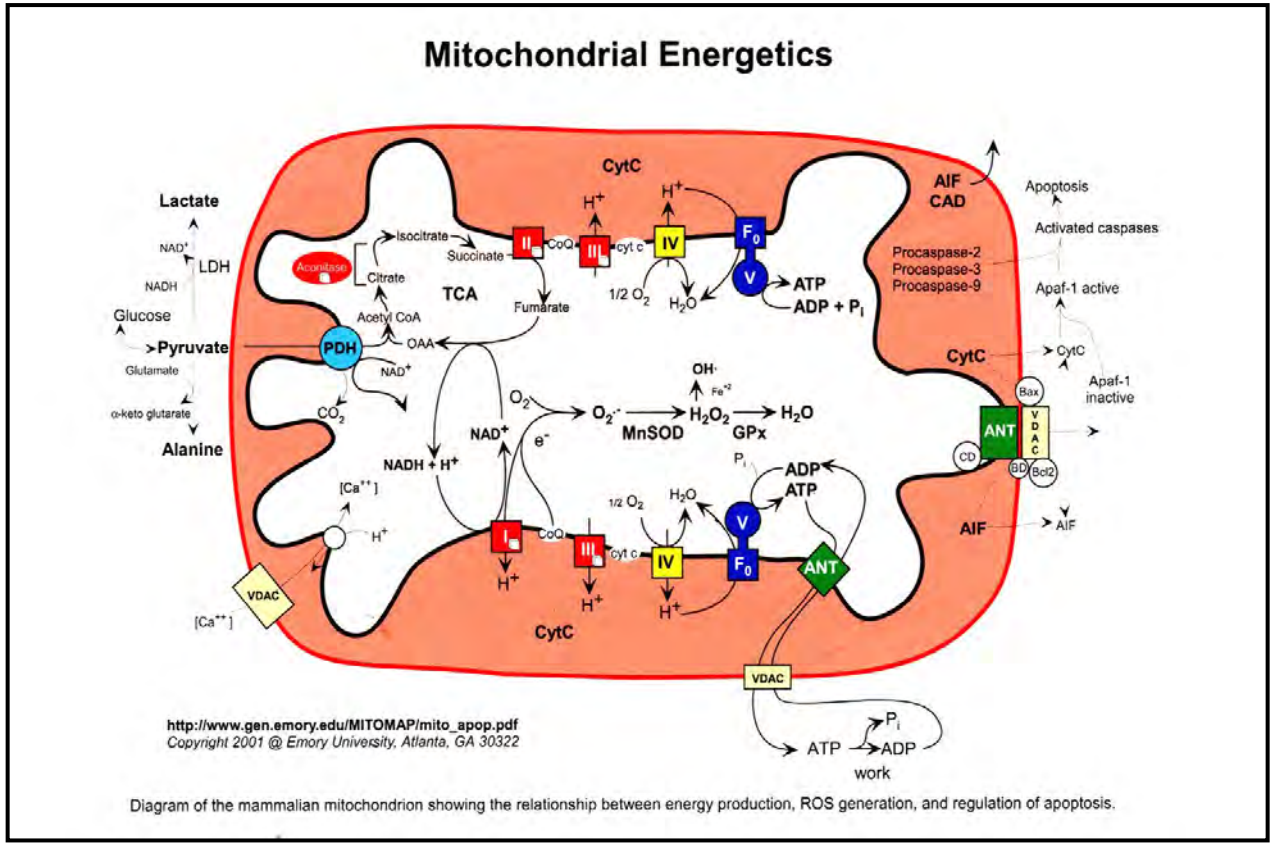
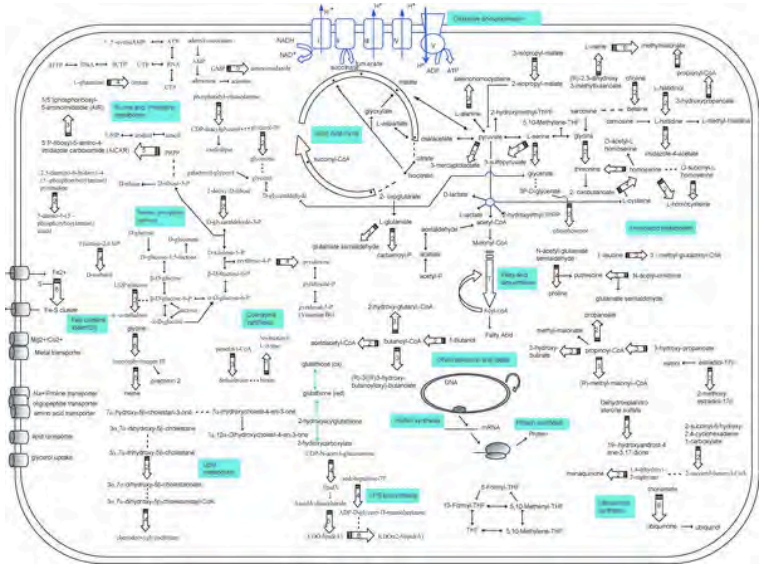
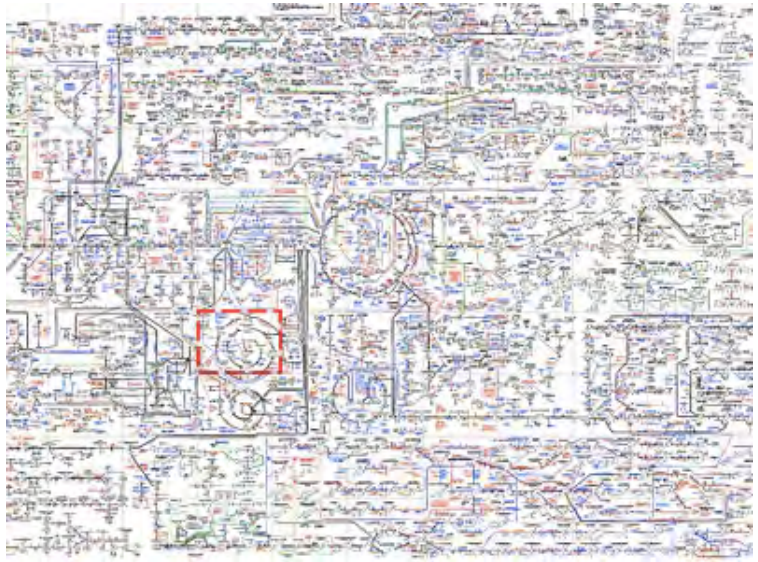


Diagram of the mammalian mitochondrion showing the relationship between energy production, ROS generation, and regulation of apoptosis.

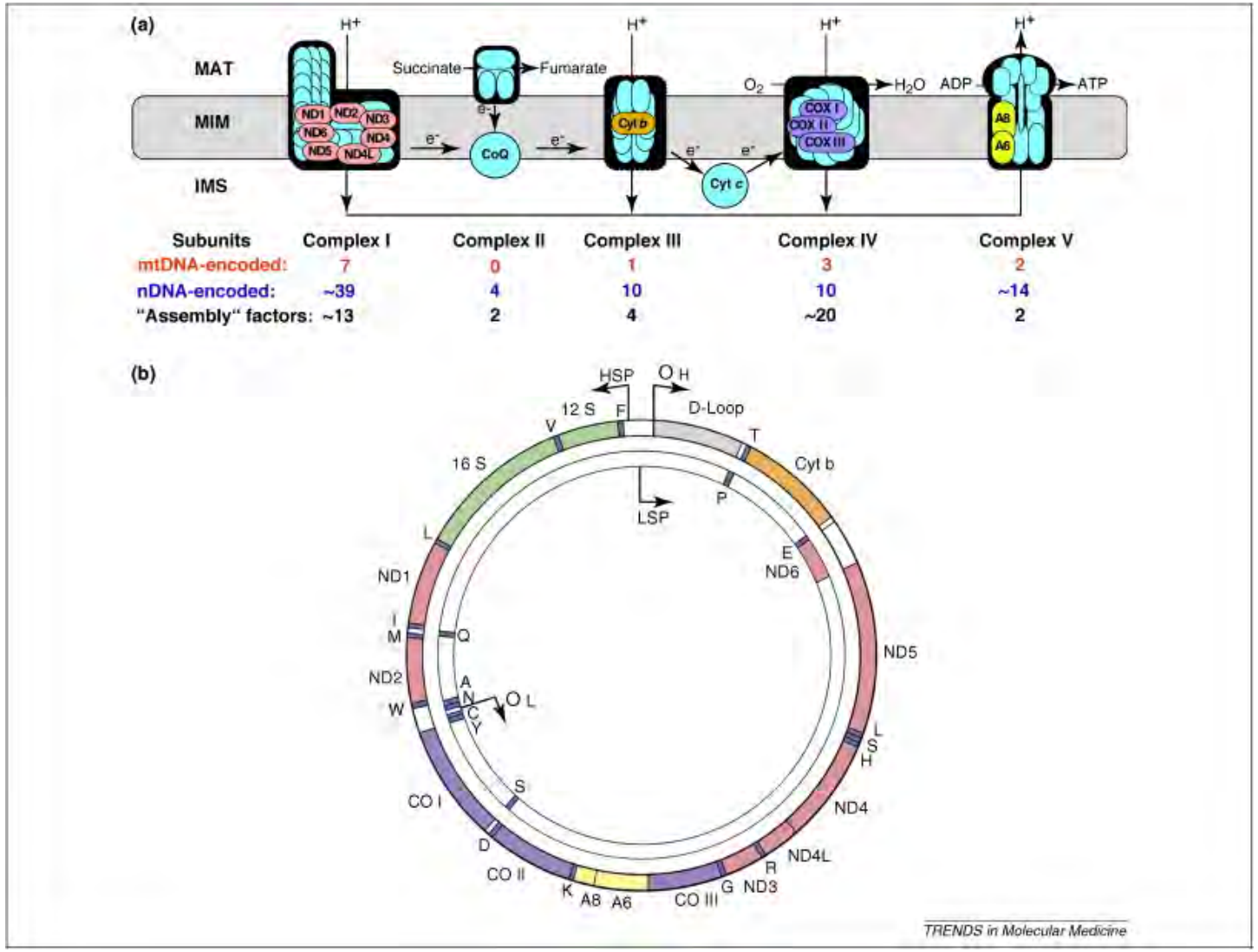




Respiratory chain (RC) and oxidative phosphorylation (OXPHOS): a pathway dependent on two genomes

Defective electron flow: increased reactive oxygen species (ROS) production and ultimately permeability transition and apoptosis

CELL DEATH



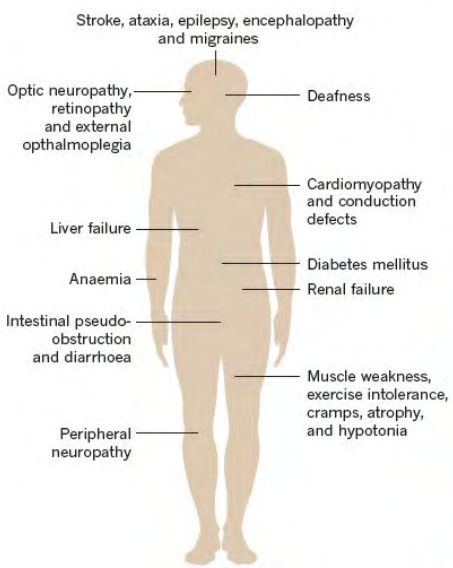
Coupling:
ATP production

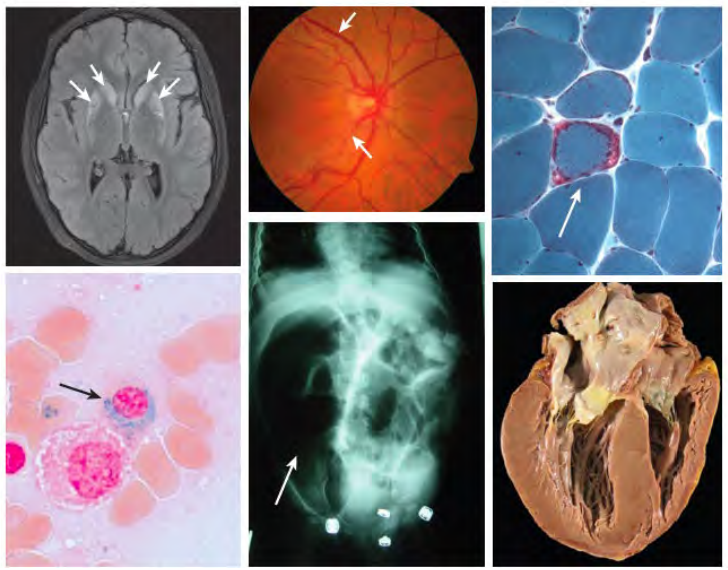
CELL SURVIVAL

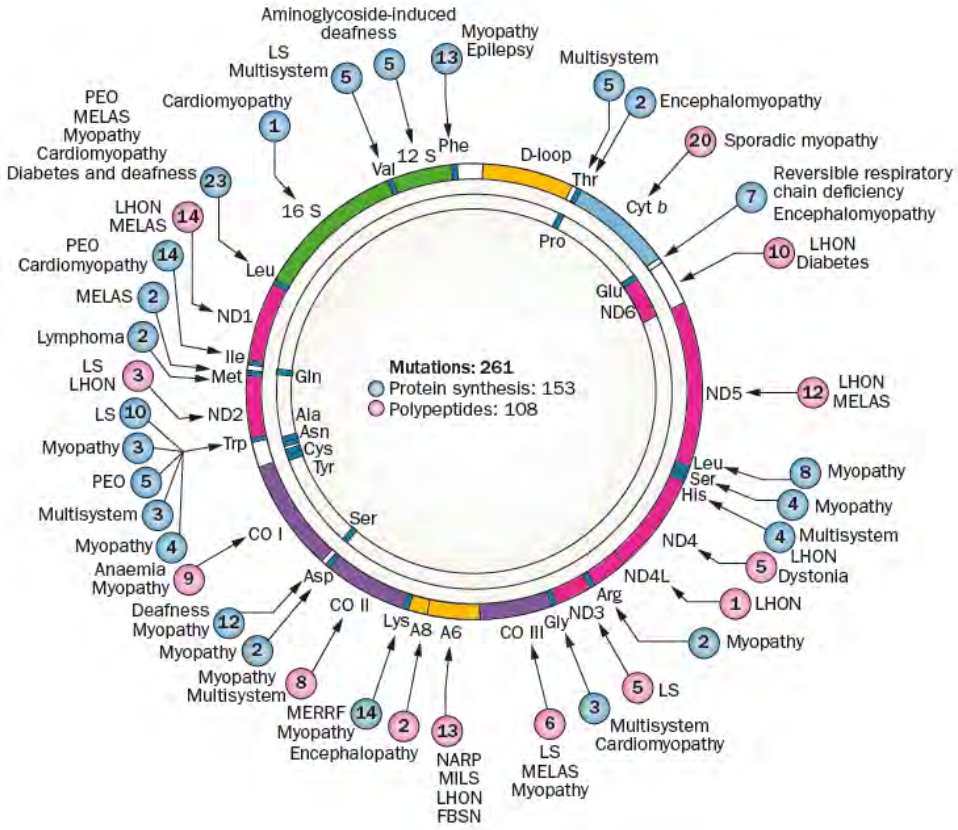
Uncoupling:
heat production

TEMPERATURE REGULATION

1988-2023: over 30 years of mitochondrial medicine







mtDNA mutation rate and «Universal heteropalsmy»

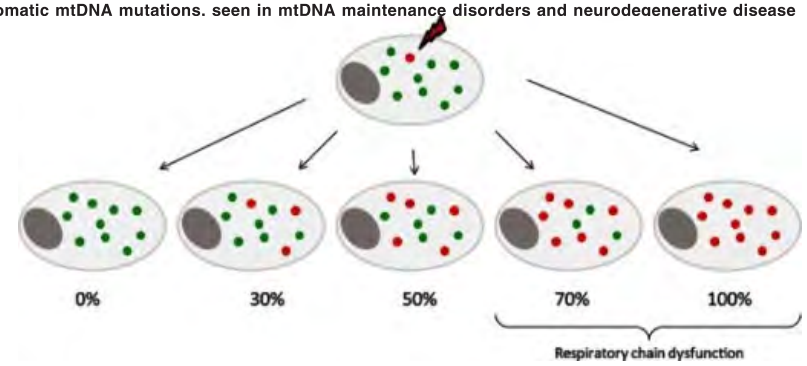
Universal heteroplasmy of human mitochondrial DNA

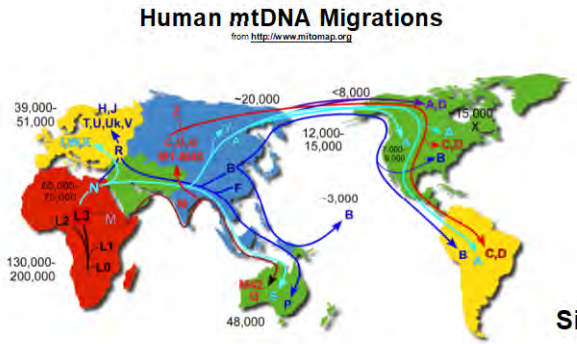
Brendan A.I. Payne[1], Ian J. Wilson[1], Patrick Yu-Wai-Man[1], Jonathan Coxhead[1], David Deehan[2], Rita Horvath[1], Robert W. Taylor[3], David C. Samuels[4], Mauro Santibanez-Koref[1] and Patrick F. Chinnery[1,*]

[1]Wellcome Trust Centre for Mitochondrial Research, Institute of Genetic Medicine, Newcastle University, Newcastle-upon-Tyne NE1 3BZ, UK [2]Institute of Cellular Medicine, Newcastle University, Newcastle-upon-Tyne NE1 7RU, UK [3]Institute for Ageing and Health, Newcastle University, Newcastle-upon-Tyne NE2 4HH, UK and [4]Centre for Human Genetics Research, Vanderbilt University, Nashville, TN 37232, USA

Received July 12, 2012; Revised and Accepted October 8, 2012

Mammalian cells contain thousands of copies of mitochondrial DNA (mtDNA). At birth, these are thought to be identical in most humans. Here, we use long read length ultra-deep resequencing-by-synthesis to interrogate regions of the mtDNA genome from related and unrelated individuals at unprecedented resolution. We show that very low-level heteroplasmic variance is present in all tested healthy individuals, and is likely to be due to both inherited and somatic single base substitutions. Using this approach, we demonstrate an increase in mtDNA mutations in the skeletal muscle of patients with a proofreading-deficient mtDNA polymerase γ due to *POLG* mutations. In contrast, we show that *OPA1* mutations, which indirectly affect mtDNA maintenance, do not increase point mutation load. The demonstration of universal mtDNA heteroplasmy has fundamental implications for our understanding of mtDNA inheritance and evolution. Ostensibly *de novo* somatic mtDNA mutations, seen in mtDNA maintenance disorders and neurodegenerative disease





TRENDS in Genetics Vol.22 No.6 June 2006

Harvesting the fruit of the human mtDNA tree

Antonio Torroni[1], Alessandro Achilli[1], Vincent Macaulay[2], Martin Richards[3] and Hans-Jürgen Bandelt[4]

Annu. Rev. Genomics Hum. Genet. 2005. 6:165–83
doi: 10.1146/annurev.genom.6.080604.162249
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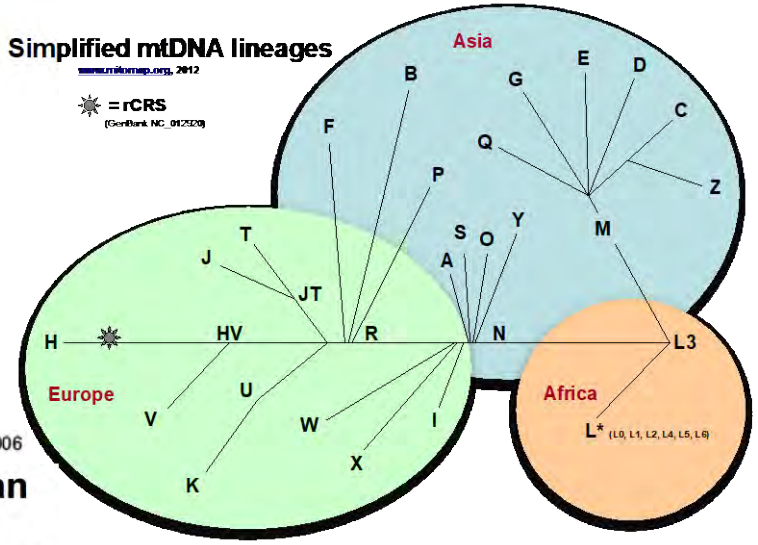
First published online as a Review in Advance on May 2, 2005

MITOCHONDRIAL DNA AND HUMAN EVOLUTION

Brigitte Pakendorf and Mark Stoneking
Max Planck Institute for Evolutionary Anthropology, D-04103 Leipzig, Germany; email: pakendorf@eva.mpg.de, stoneking@eva.mpg.de



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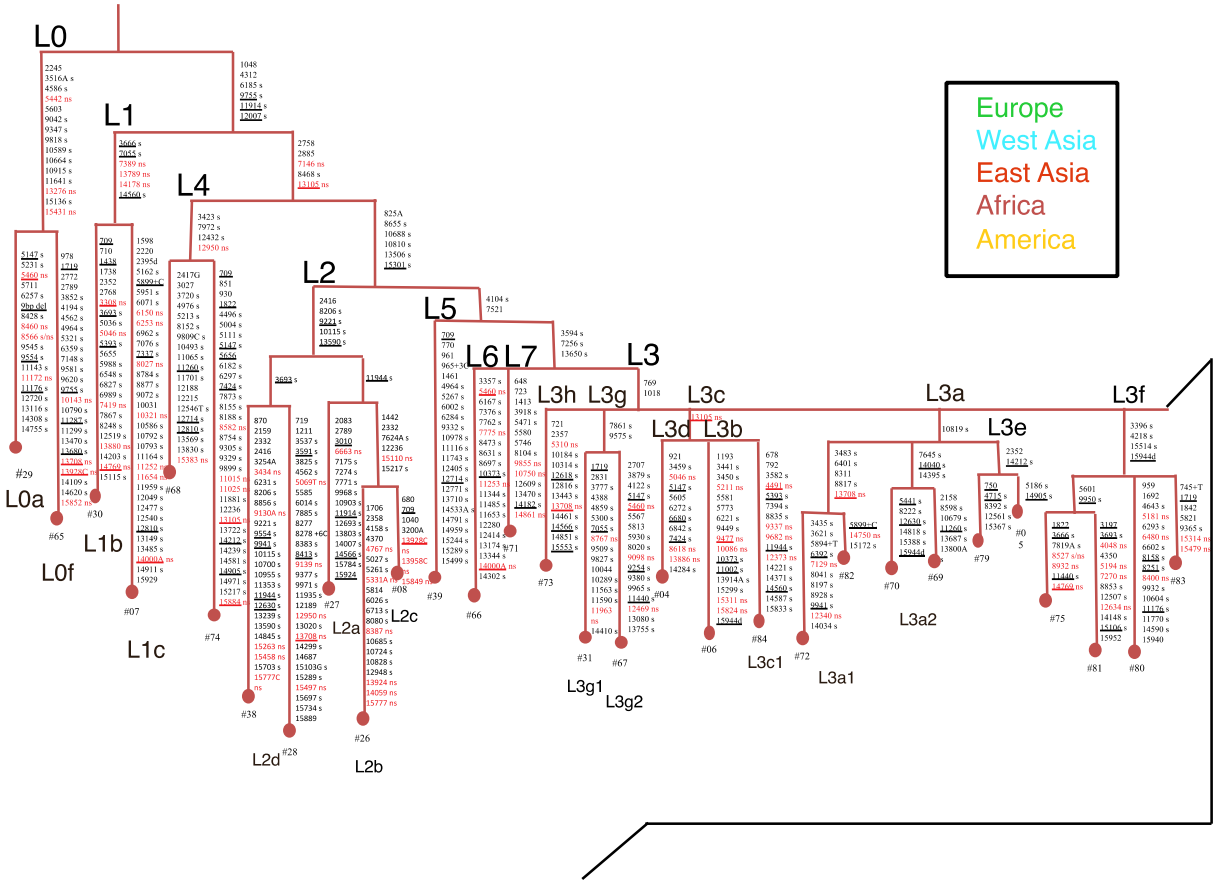
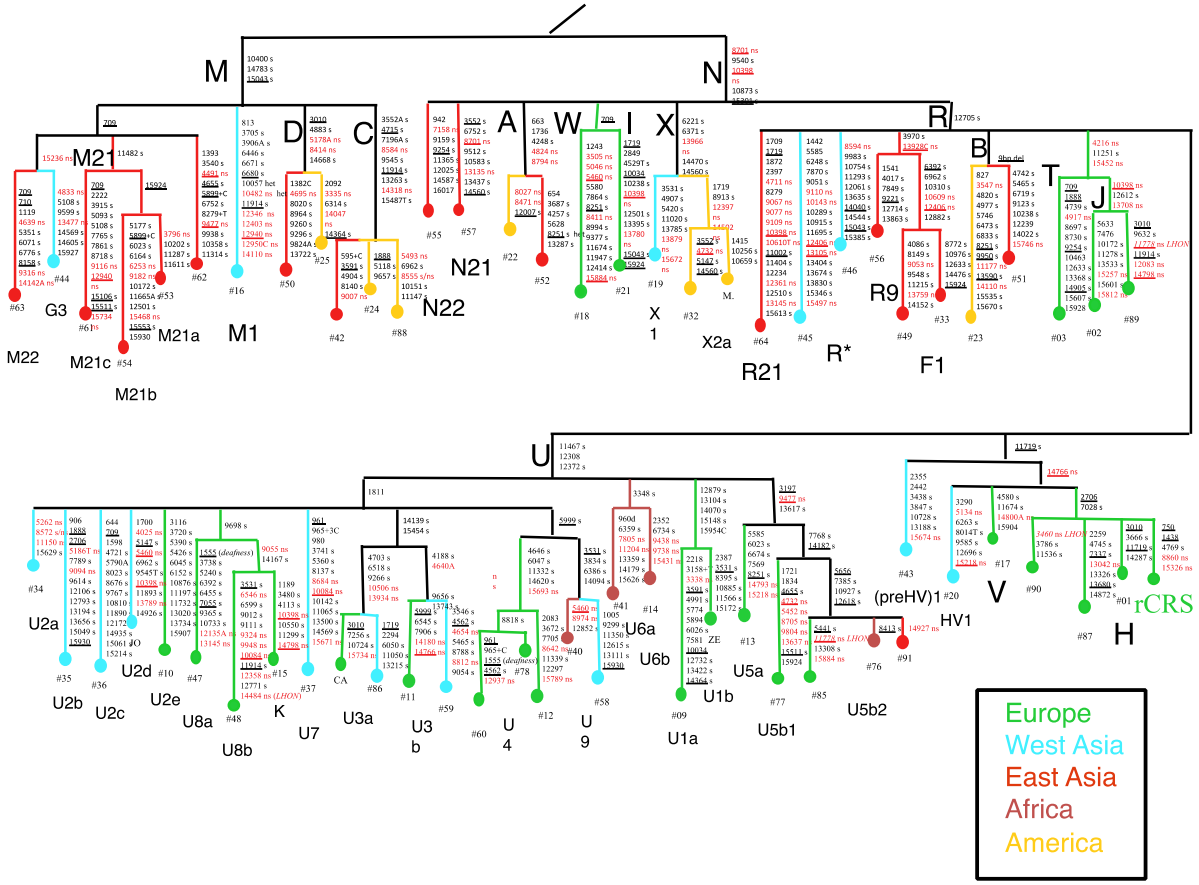
mtDNA haplogroups (related haplotypes)



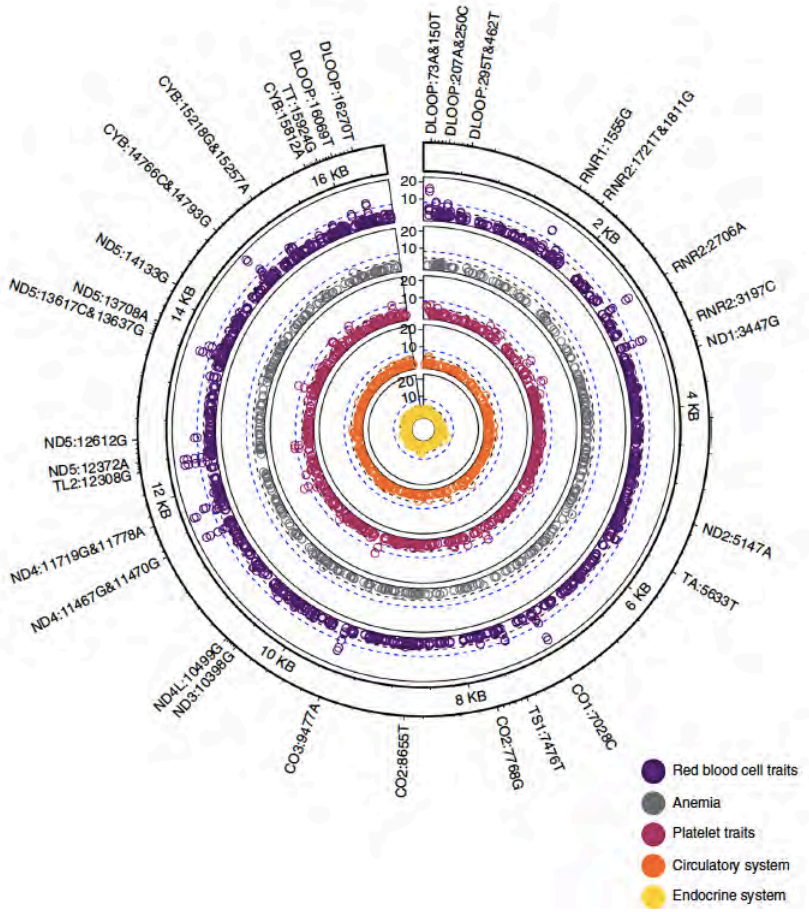


Impact of mtDNA haplogroup-related variants on common traits and diseases

ARTICLES
https://doi.org/10.1038/s41588-021-00868-1
nature genetics
Check for updates

An atlas of mitochondrial DNA genotype–phenotype associations in the UK Biobank

Ekaterina Yonova-Doing[1,2,6], Claudia Calabrese[3,4,6], Aurora Gomez-Duran[3,4,5], Katherine Schon[3,4], Wei Wei[3,4], Savita Karthikeyan[1], Patrick F. Chinnery[3,4,7] ✉ and Joanna M. M. Howson[1,2,7] ✉

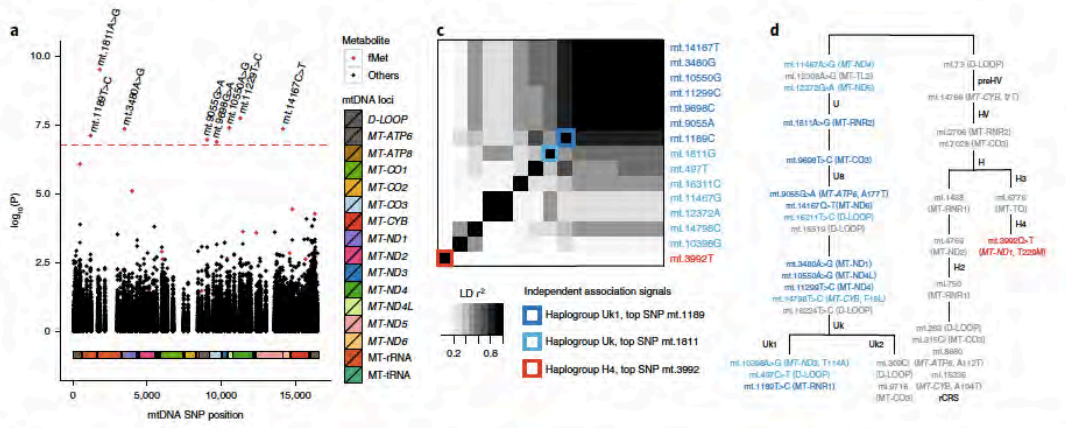


Impact of mtDNA haplogroup-related variants on common traits and diseases

ARTICLES
https://doi.org/10.1038/s41591-021-01441-3
nature medicine
Check for updates

Mitochondrial DNA variants modulate *N*-formylmethionine, proteostasis and risk of late-onset human diseases

Na Cai[1,2,3,22], Aurora Gomez-Duran[4,5,6,22], Ekaterina Yonova-Doing[7,8], Kousik Kundu[1], Annette I. Burgess[9], Zoe J. Golder[4,5], Claudia Calabrese[4,5], Marc J. Bonder[2,10], Marta Camacho[4], Rachael A. Lawson[11], Lixin Li[9], Caroline H. Williams-Gray[4], ICICLE-PD Study Group*, Emanuele Di Angelantonio[7,12,13,14], David J. Roberts[13,15,16], Nick A. Watkins[17], Willem H. Ouwehand[1,12,17,18], Adam S. Butterworth[7,12,13,14], Isobel D. Stewart[19], Maik Pietzner[19], Nick J. Wareham[19], Claudia Langenberg[19], John Danesh[1,7,12,13,14], Klaudia Walter[1], Peter M. Rothwell[9], Joanna M. M. Howson[7,8,23], Oliver Stegle[2,10,20,23] ✉, Patrick F. Chinnery[4,5,23] ✉ and Nicole Soranzo[1,12,13,18,21,23] ✉



SNP						Discovery (INTERVAL)						Replication (EPIC)		
						LMM			CMS			LMM		
bp	Gene	A_1	A_0	A_{1freq}	Annot	β	s.d.	P	β	s.d.	P	β	s.d.	P
497	*D-LOOP*	T	C	0.050	D-loop	0.144	0.029	8.33×10^{-7}	0.039	0.007	5.67×10^{-9}	0.100	0.022	4.74×10^{-6}
1,189	*MT-RNR1*	C	T	0.072	12S rRNA	0.133	0.025	7.57×10^{-8}	0.057	0.007	7.36×10^{-18}		Not genotyped	
1,811	*MT-RNR2*	G	A	0.129	16S rRNA	0.120	0.019	3.03×10^{-10}	0.057	0.007	4.63×10^{-18}		Not genotyped	
3,480	*MT-ND1*	G	A	0.087	syn:K58K	0.125	0.023	4.32×10^{-8}	0.057	0.007	1.44×10^{-17}	0.076	0.017	3.33×10^{-6}
3,992	*MT-ND1*	T	C	0.023	non-syn:T229M	−0.190	0.042	7.86×10^{-6}	−0.054	0.007	6.05×10^{-16}	−0.137	0.033	3.93×10^{-5}
9,055	*MT-ATP6*	A	G	0.089	non-syn:A177T	0.119	0.022	1.08×10^{-7}	0.054	0.007	2.47×10^{-16}	0.070	0.016	2.13×10^{-5}
9,698	*MT-CO3*	C	T	0.089	syn:L164L	0.119	0.023	1.30×10^{-7}	0.056	0.007	2.05×10^{-17}	0.079	0.017	3.23×10^{-6}
10,398	*MT-ND3*	G	A	0.216	non-syn:T114S	0.048	0.016	2.32×10^{-3}	0.038	0.007	8.68×10^{-9}		Not genotyped	
10,550	*MT-ND4L*	G	A	0.086	syn:M27M	0.126	0.023	4.02×10^{-8}	0.058	0.007	3.59×10^{-18}	0.079	0.017	2.82×10^{-6}
11,229	*MT-ND4*	C	T	0.087	syn:T180T	0.128	0.023	1.78×10^{-8}	0.058	0.007	1.80×10^{-18}		Not genotyped	
11,467	*MT-ND4*	G	A	0.229	syn:L236L	0.056	0.015	2.39×10^{-4}	0.040	0.007	1.50×10^{-9}		Not genotyped	
12,372	*MT-ND5*	A	G	0.229	syn:L12L	0.056	0.015	2.67×10^{-4}	0.040	0.007	1.82×10^{-9}		Not genotyped	
14,167	*MT-ND6*	T	C	0.086	syn:E169E	0.125	0.023	4.32×10^{-8}	0.057	0.007	1.44×10^{-17}	0.076	0.017	7.62×10^{-6}
14,798	*MT-CYB*	C	T	0.166	non-syn:F18L	0.071	0.017	3.66×10^{-5}	0.039	0.007	3.92×10^{-9}	0.044	0.013	6.83×10^{-4}
16,311	*D-LOOP*	C	T	0.088	D-loop	0.070	0.017	5.39×10^{-5}	0.050	0.007	3.60×10^{-12}		Not genotyped	

mtDNA, immune system and inflammation: a new chapter

ANNUAL REVIEWS

Annual Review of Biochemistry

Mitochondrial DNA Release in Innate Immune Signaling

Laura E. Newman and Gerald S. Shadel

Salk Institute for Biological Studies, La Jolla, California, USA; email: gshadel@salk.edu

frontiers in Cell and Developmental Biology

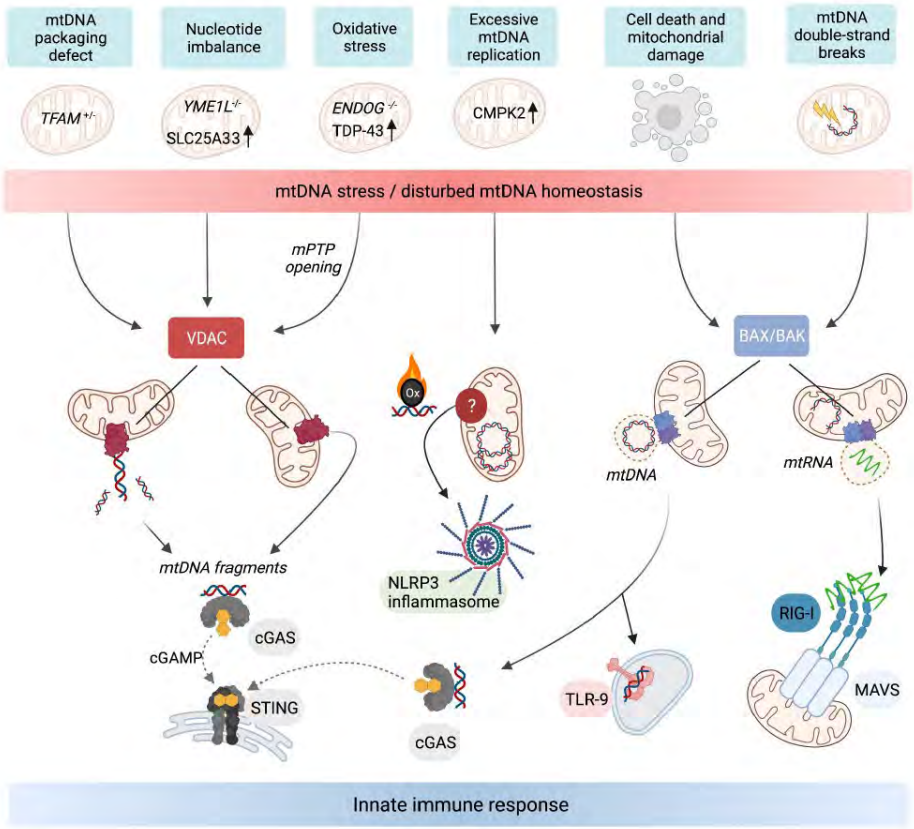
REVIEW

published: 27 July 2021

doi: 10.3389/fcell.2021.720480

Metabolism and Innate Immunity Meet at the Mitochondria

Amir Bahat[1†], Thomas MacVicar[1†] and Thomas Langer[1,2]*



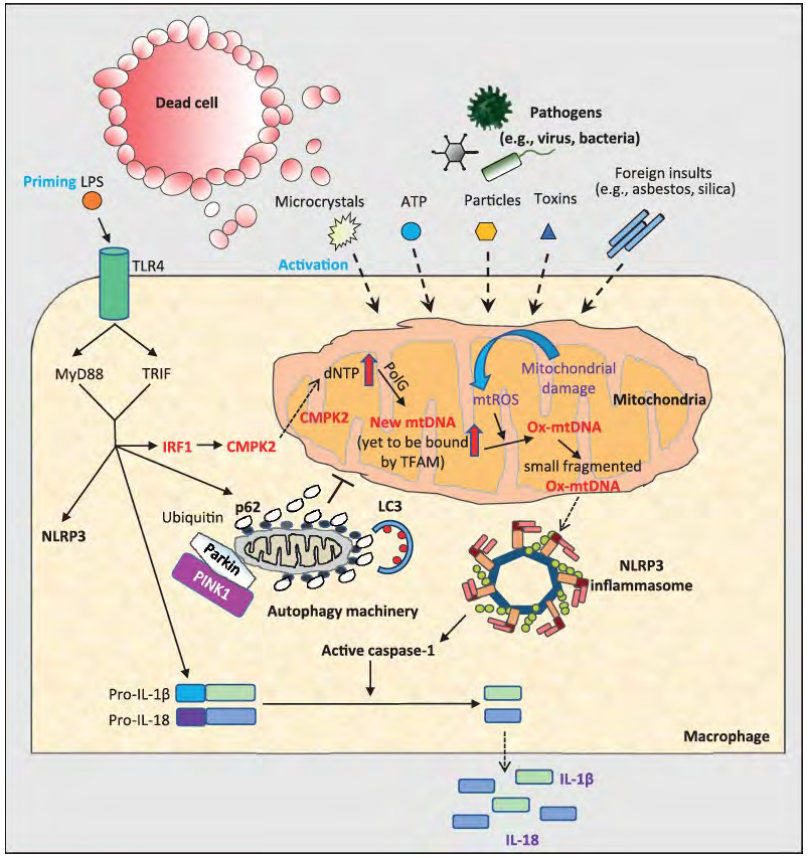
nature

Vol 464|4 March 2010|doi:10.1038/nature08780

LETTERS

Circulating mitochondrial DAMPs cause inflammatory responses to injury

Qin Zhang[1], Mustafa Raoof[1], Yu Chen[1], Yuka Sumi[1], Tolga Sursal[1], Wolfgang Junger[1], Karim Brohi[2], Kiyoshi Itagaki[1] & Carl J. Hauser[1]



mtDNA haplogroup H protects from infections

www.thelancet.com Vol 366 December 17/24/31, 2005

Mitochondrial DNA and survival after sepsis: a prospective study

Simon V Baudouin, David Saunders, Watcharee Tiangyou, Joanna L Elson, Jayne Poynter, Angela Pyle, Sharon Keers, Douglass M Turnbull, Neil Howell, Patrick F Chinnery

Summary

Background Human genome evolution has been shaped by infectious disease. Although most genetic studies have focused on the immune system, recovery after sepsis is directly related to physiological reserve that is critically dependent on mitochondrial function. We investigated whether haplogroup H, the most common type of mitochondrial DNA (mtDNA) in Europe, contributes to the subtle genetic variation in survival after sepsis.

Methods In a prospective study, we included 150 individuals who were sequentially admitted to the intensive care unit in a hospital in Newcastle upon Tyne, UK. After clinical data were obtained, patients underwent mtDNA haplotyping by analysis with PCR and restriction fragment length polymorphism. As endpoints, we used death during the 6-month period or survival at 6 months.

Findings Follow-up was complete for all study participants, although the haplotype of two patients could not be reliably determined. On admission to the intensive care unit, the frequency of mtDNA haplogroup H in study patients did not differ between study patients admitted with severe sepsis and 542 age-matched controls from the northeast of England. MtDNA haplogroup H was a strong independent predictor of outcome during severe sepsis, conferring a 2·12-fold (95% CI 1·02–4·43) increased chance of survival at 180 days compared with individuals without the haplogroup H.

Interpretation Although haplogroup H is the most recent addition to the group of European mtDNA, paradoxically it is also the most common. Increased survival after sepsis provides one explanation for this observation. MtDNA haplotyping offers a new means of risk stratification of patients with severe infections, which suggests new avenues for therapeutic intervention.

Mitochondrial proteins encoded by the nuclear genome

Published online 11 November 2020 *Nucleic Acids Research, 2021, Vol. 49, Database issue* **D1541–D1547**
doi: 10.1093/nar/gkaa1011

MitoCarta3.0: an updated mitochondrial proteome now with sub-organelle localization and pathway annotations

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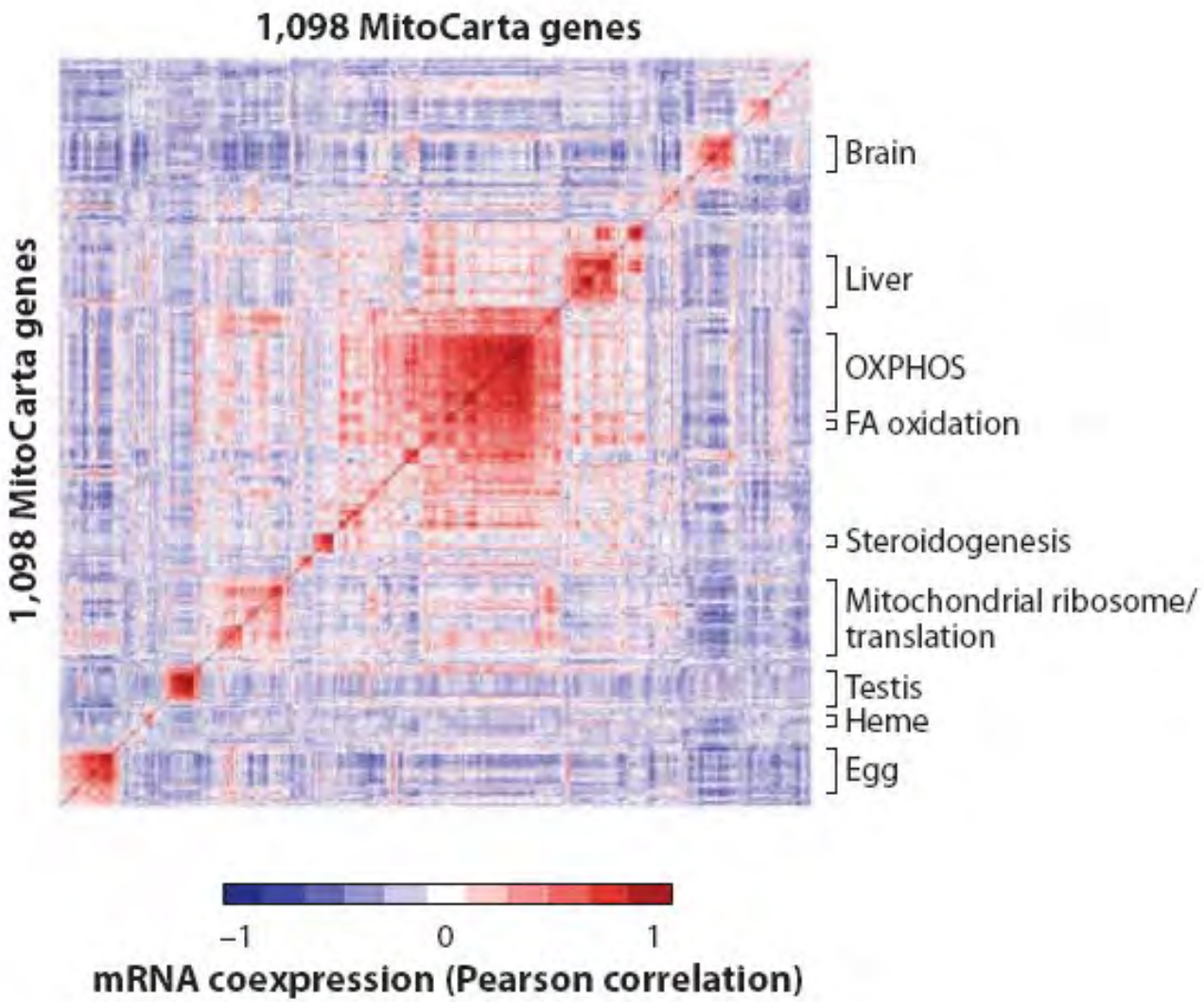
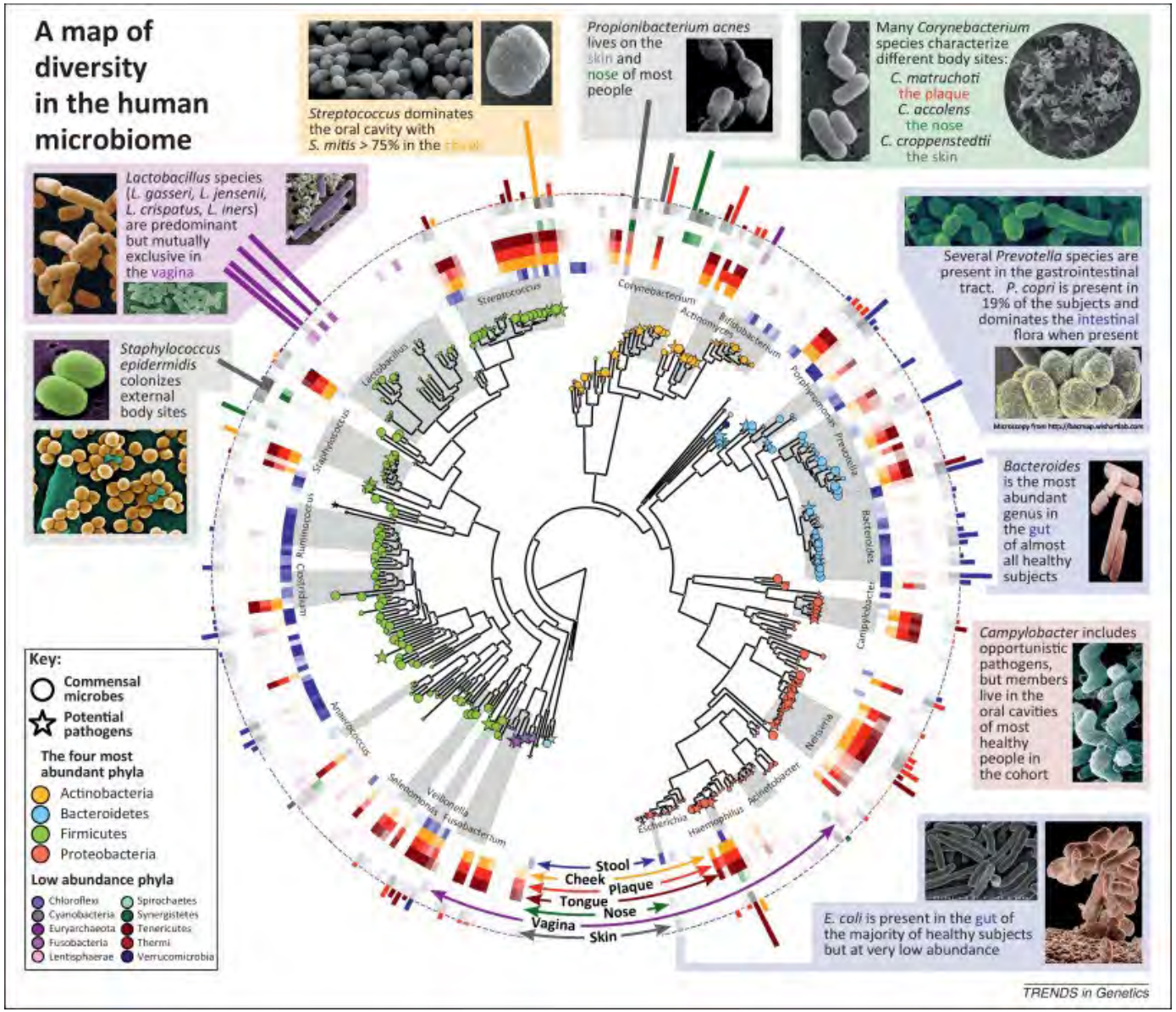
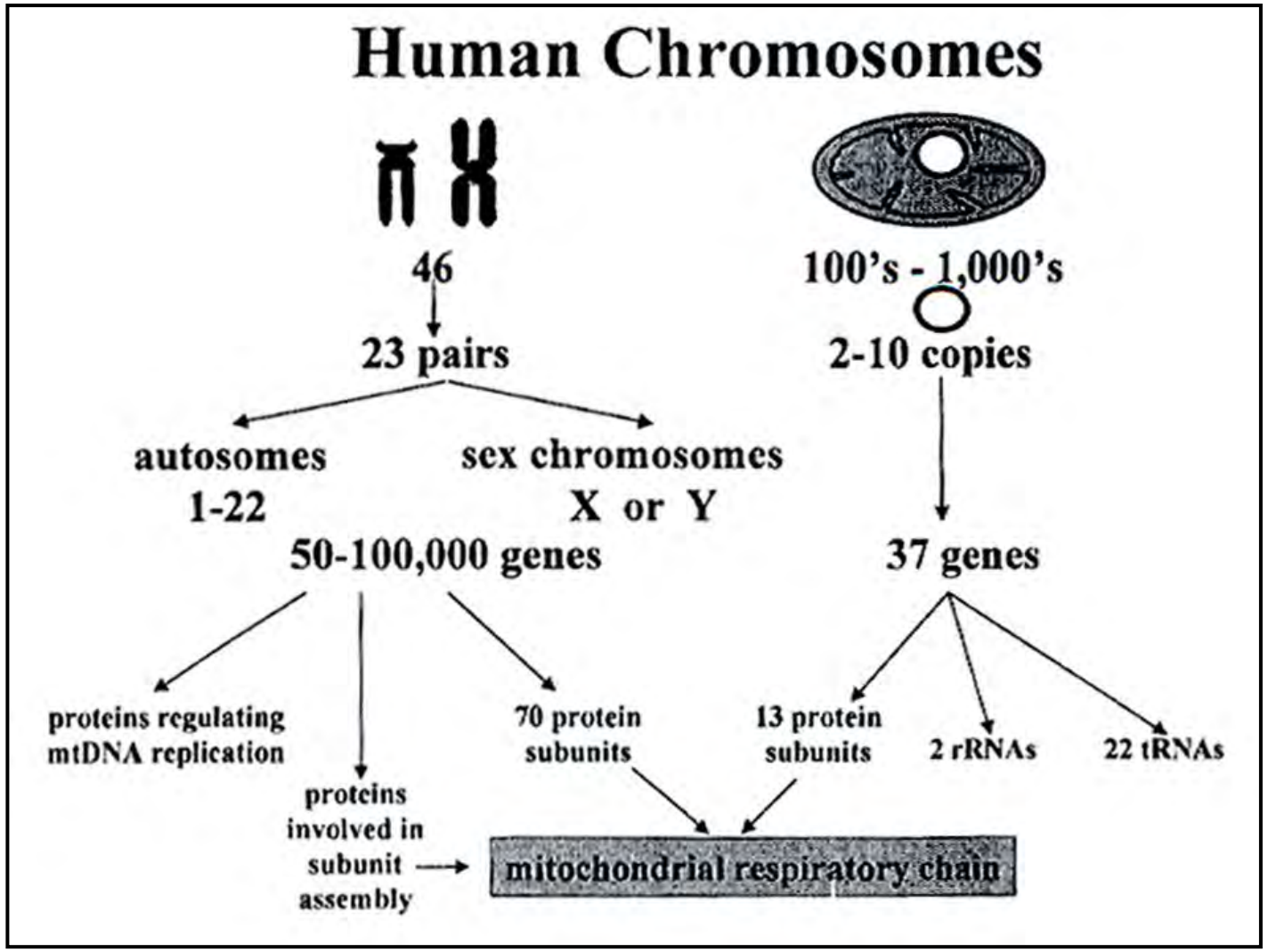


Human microbiome: a complex metagenome



Human genetics…..and may be more



Review Article

The Three Genetics (Nuclear DNA, Mitochondrial DNA, and Gut Microbiome) of Longevity in Humans Considered as Metaorganisms

Paolo Garagnani,[1,2,3] Chiara Pirazzini,[1,2] Cristina Giuliani,[4] Marco Candela,[5] Patrizia Brigidi,[5] Federica Sevini,[1,2] Donata Luiselli,[4] Maria Giulia Bacalini,[1,2] Stefano Salvioli,[1,2] Miriam Capri,[1,2] Daniela Monti,[6] Daniela Mari,[7,8] Sebastiano Collino,[9] Massimo Delledonne,[10] Patrick Descombes,[11] and Claudio Franceschi[1,2,12,13]

In this view, human being must be considered as "metaorganism" and a more holistic approach is necessary to grasp the complex dynamics of the interaction between the environment and nDNA-mtDNA-GM of the host during ageing.

«Genetics loads the gun, but environment pulls the trigger»…the EXPOSOME paradigm

How the 3 genomes may interact with environment?

- **Nuclear DNA (nDNA):** somatic mutagenesis and changes in epigenetic (methylation) profile (epiDNA)

- **Mitochondrial DNA (mtDNA):** selection of germline inherited mutagenesis (universal heteroplasmy and mtDNA haplogropus) and somatic mutagenesis, as well as adaptation by adjusting the mtDNA copy number

- **Microbiome:** shifts across the 3 possible microbiome functional profiles as *mutualists* (symbiotically beneficial), *commensalists* (of neither harm nor benefit), or *pathogens* (detrimental to the host)

Is there any special relationship between mitochondria (mtDNA) and bacteria from the microbiome?

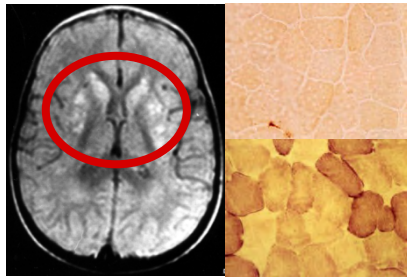
- Metabolic dialog

- Genomic (mtDNA) dialog

Examples from rare mitochondrial diseases:

ETHE1 encephalomyopathy and MNGIE (MyoNeuroGastroIntestinal Encephalomyopathy)

The case of the rare human disorder «Ethylmalonic Encephalopathy» (ETHE1 Deficiency)

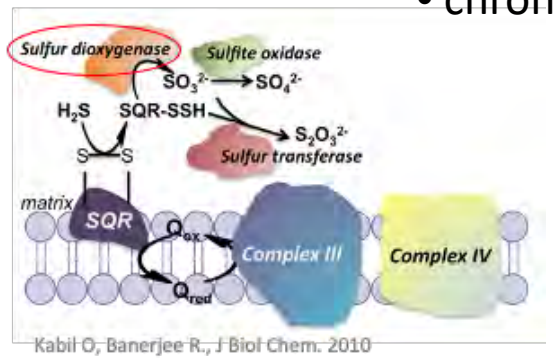


ETHE1

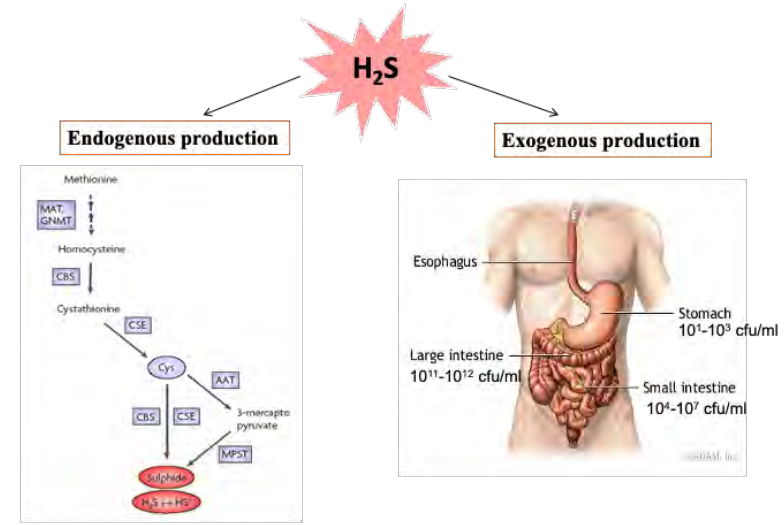
Clinical features:

- hypotonia
- developmental delay
- brainstem lesions
- acrocyanosis
- petechiae
- chronic diarrhea

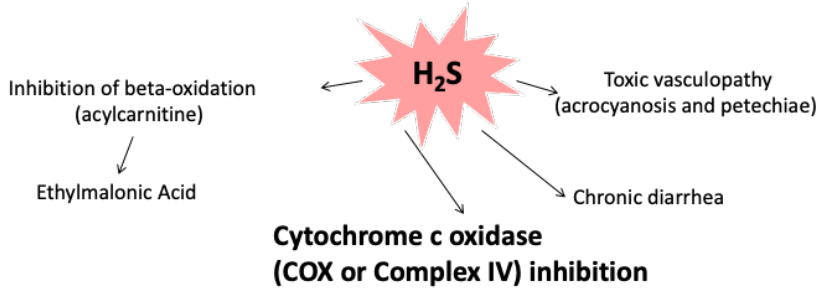
- mitochondrial matrix protein
- links to iron
- sulfur-dioxygenase activity



Kabil O, Banerjee R., J Biol Chem. 2010



Szabo, Nat Rev Drug Discov 2007



When produced at excessive concentrations by local microbiota, H_2S may cause mucus disruption and inflammation and contribute to development of cancer. In contrast, low levels of endogenous or exogenous H_2S directly stabilize mucus layers, prevent fragmentation and adherence of the microbiota biofilm to the epithelium, inhibit the release of invasive pathobionts, and help resolve inflammation and tissue injury. Although scarce, research findings suggest that dietary H_2S obtained from plants or ingestion of the H_2S precursor, L-cysteine, may also modulate the abundance and function of microbiota.

Human microbiome: is it interacting with mitochondria in physiology and disease? Lessons from C. Elegans….

Cell

Leading Edge
Previews

Microbiome and Longevity: Gut Microbes Send Signals to Host Mitochondria

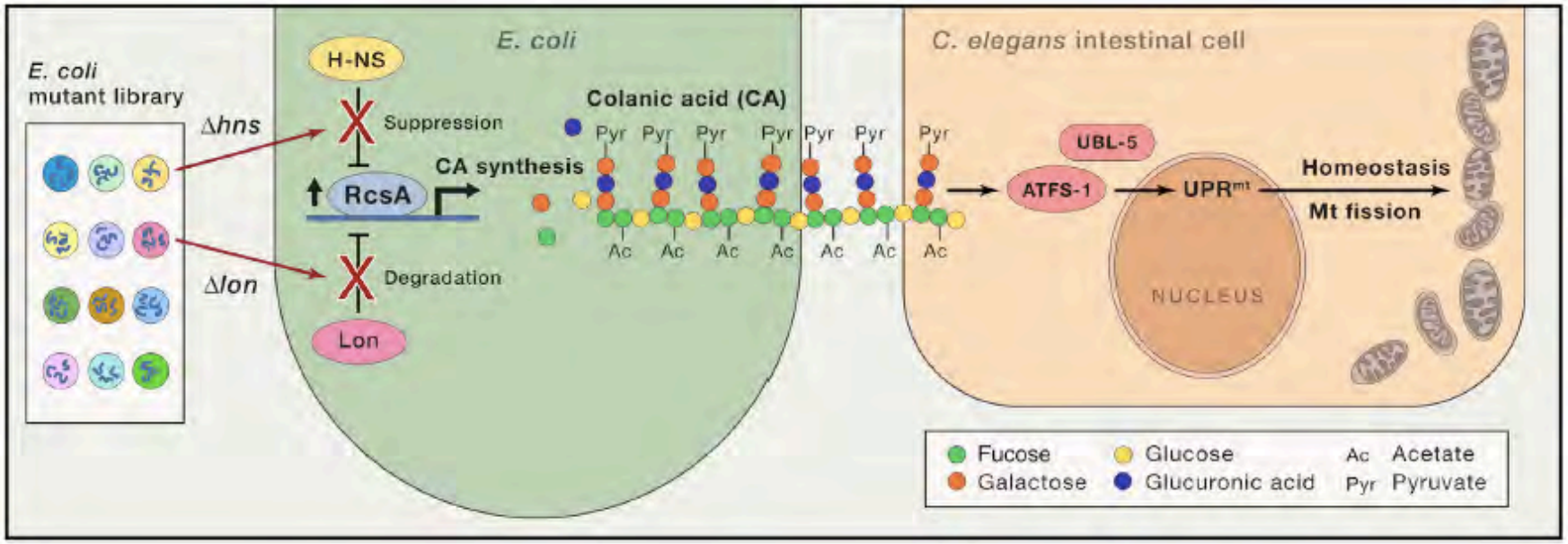
Jan Gruber[1,2] and Brian K. Kennedy[1,3,4,*]

Article

Cell

Microbial Genetic Composition Tunes Host Longevity

Bing Han,[1,2] Priya Sivaramakrishnan,[2] Chih-Chun J. Lin,[1,2] Isaiah A.A. Neve,[1,2] Jingquan He,[3] Li Wei Rachel Tay,[3] Jessica N. Sowa,[1,2] Antons Sizovs,[4] Guangwei Du,[3] Jin Wang,[4] Christophe Herman,[2,5] and Meng C. Wang[1,2,5,6,*]



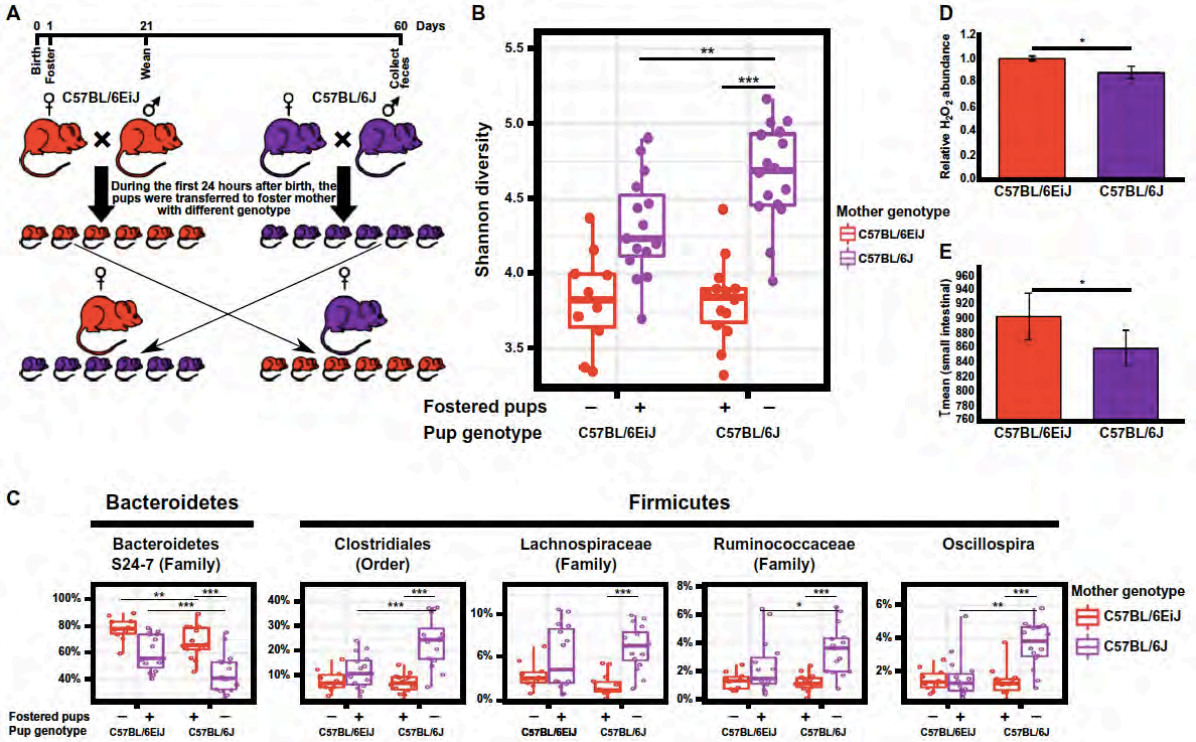
SCIENCE SIGNALING | RESEARCH ARTICLE

HOST-MICROBE INTERACTIONS

Host mitochondria influence gut microbiome diversity: A role for ROS

Tal Yardeni[1], Ceylan E. Tanes[2], Kyle Bittinger[2], Lisa M. Mattei[2], Patrick M. Schaefer[1], Larry N. Singh[1], Gary D. Wu[3], Deborah G. Murdock[1], Douglas C. Wallace[1,4]*

Inherited host genotype determines the gut microbiome composition.



Ma et al. BMC Genomics 2014, 15:257
http://www.biomedcentral.com/1471-2164/15/257

BMC Genomics

RESEARCH ARTICLE Open Access

mtDNA haplogroup and single nucleotide polymorphisms structure human microbiome communities

Jun Ma[1,2], Cristian Coarfa[2], Xiang Qin[2], Penelope E Bonnen[2], Aleksandar Milosavljevic[2], James Versalovic[2,3] and Kjersti Aagaard[1,2*]

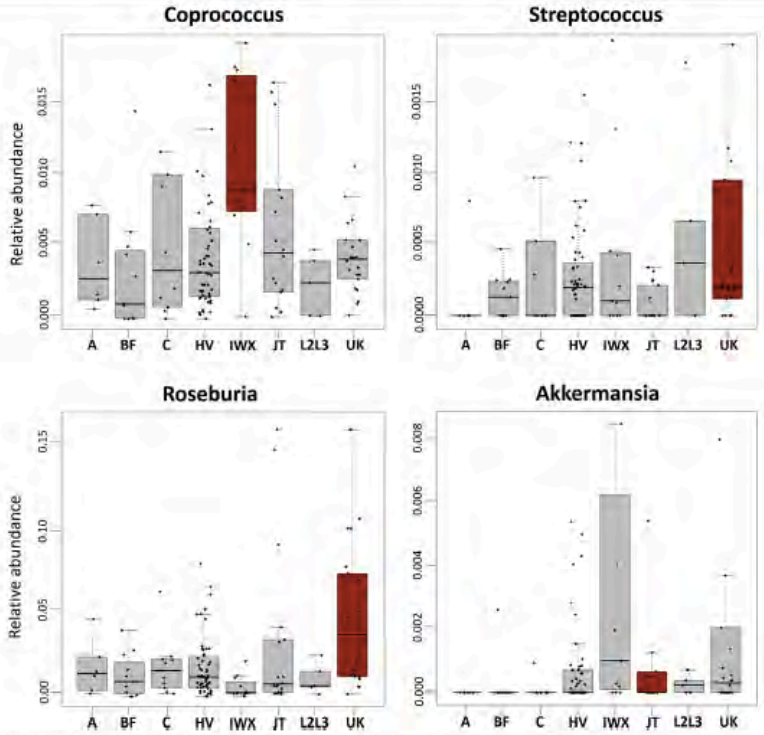


Figure 2 The distribution of four genus level abundance over haplogroups in stool samples. The Y-axis shows the relative abundance of the genus in corresponding haplogroups. The haplogroup box marked in red is the haplogroup associated with corresponding genus, which is discovered by multiple linear regression using genus level relative abundance as dependent variable and using haplogroup assignment, clinical metadata as independent variables. The number of samples in each haplogroup is parenthetically annotated, A(6), BF(11), C(10), HV(56), IWX(11), JT(18), L2L3(5), UK(22).

In conclusion

- We need to investigate the yet essentially unexplored dialog between mitochondria (mtDNA haplogroups) and bacteria from the microbiome in health, disease and aging (H_2S, colanic acid, ROS ……)….and interaction with Exposome/Environment

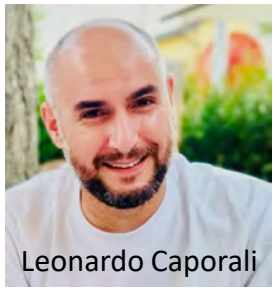
- We have the opportunity to start exploring this relationship with two H2020 projects in Bologna: ORCHESTRA (SARS-Cov-2) and TRIGGER (climate changes and heat waves)

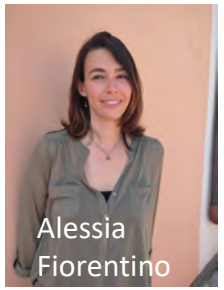
- The 3 genomes versus environment: the new paradigm for future studies of our «***Healthy Planet***»

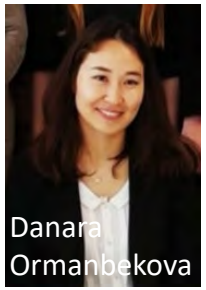
Thanks for your attention

Lab Programma di Neurogenetica

ORCHESTRA TEAM


Leonardo Caporali


Alessia Fiorentino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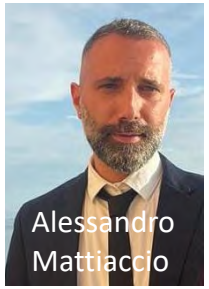
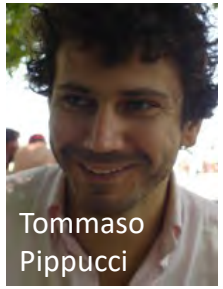
Patrizia Brigidi


Alessandro Mattiaccio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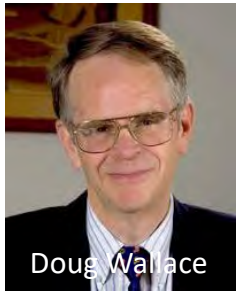
mtDNA HAPLOGROUPS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Antonio Torroni

Patrick Chinnery