30 years of Mitochondrial Medicine

(a brief history of mtDNA and a last chapter)

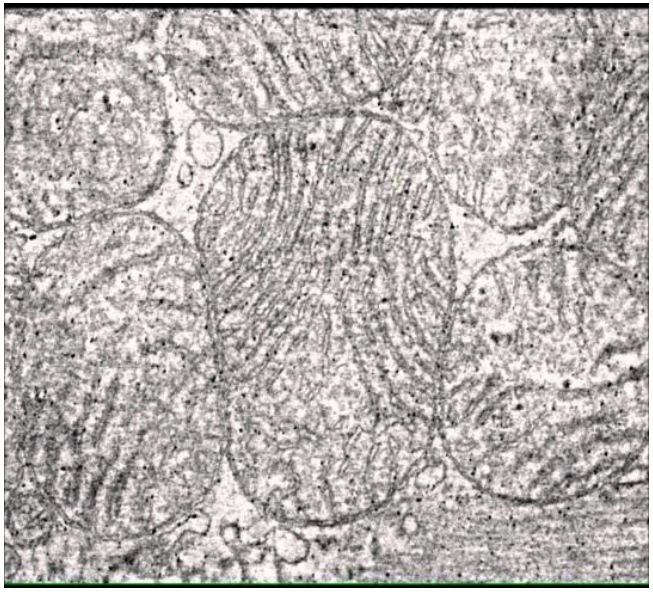
Valerio Carelli MD, PhD

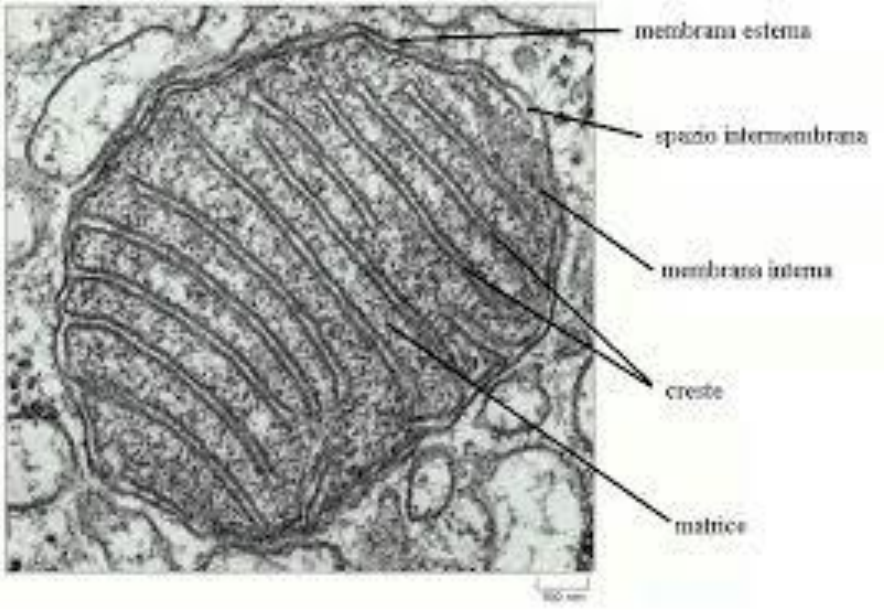
IRCCS Institute of Neurological Sciences of Bologna (ISNB), Bellaria Hospital, Bologna, Italy

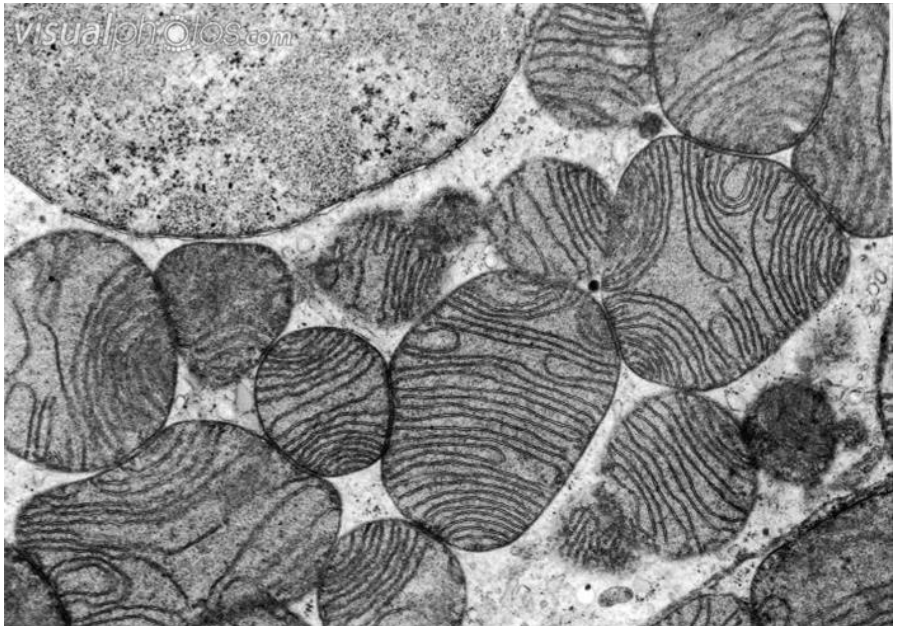
Neurology Unit, Department of Biomedical and NeuroMotor Sciences (DiBiNeM), University of Bologna, Bologna, Italy

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

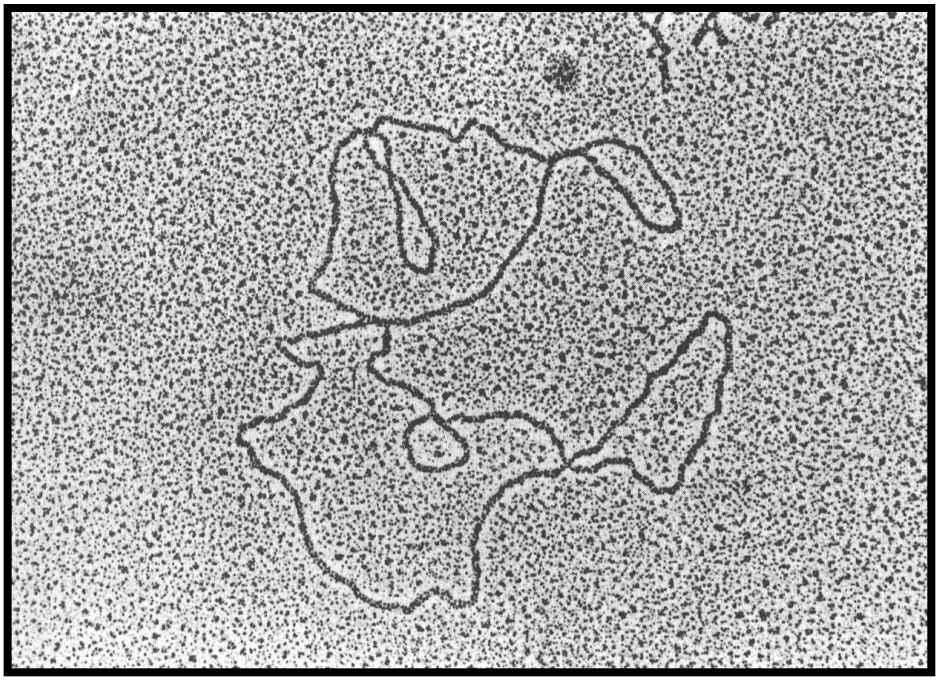
MITOCHONDRIA







Mitochondrial DNA (mtDNA): 16.569 bp



INTRAMITOCHONDRIAL FIBERS
WITH DNA CHARACTERISTICS

I. Fixation and Electron Staining Reactions

MARGIT M. K. NASS, Ph.D., and SYLVAN NASS, Ph.D.

From the Wenner-Gren Institute for Experimental Biology, Stockholm University, Stockholm, Sweden

INTRAMITOCHONDRIAL FIBERS
WITH DNA CHARACTERISTICS

II. Enzymatic and Other Hydrolytic Treatments

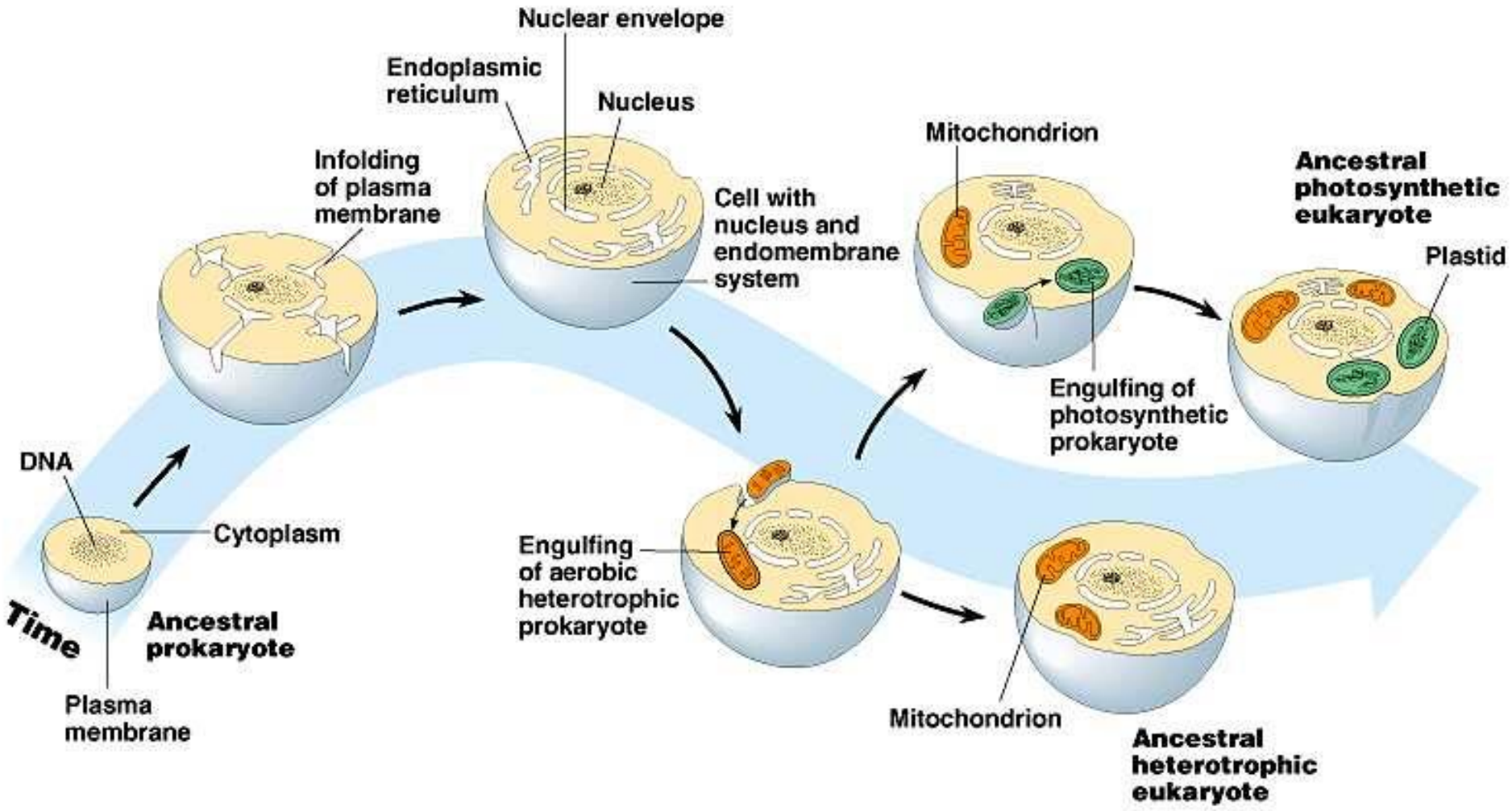
SYLVAN NASS, Ph.D., and MARGIT M. K. NASS, Ph.D.

From the Wenner-Gren Institute for Experimental Biology, Stockholm University, Stockholm, Sweden

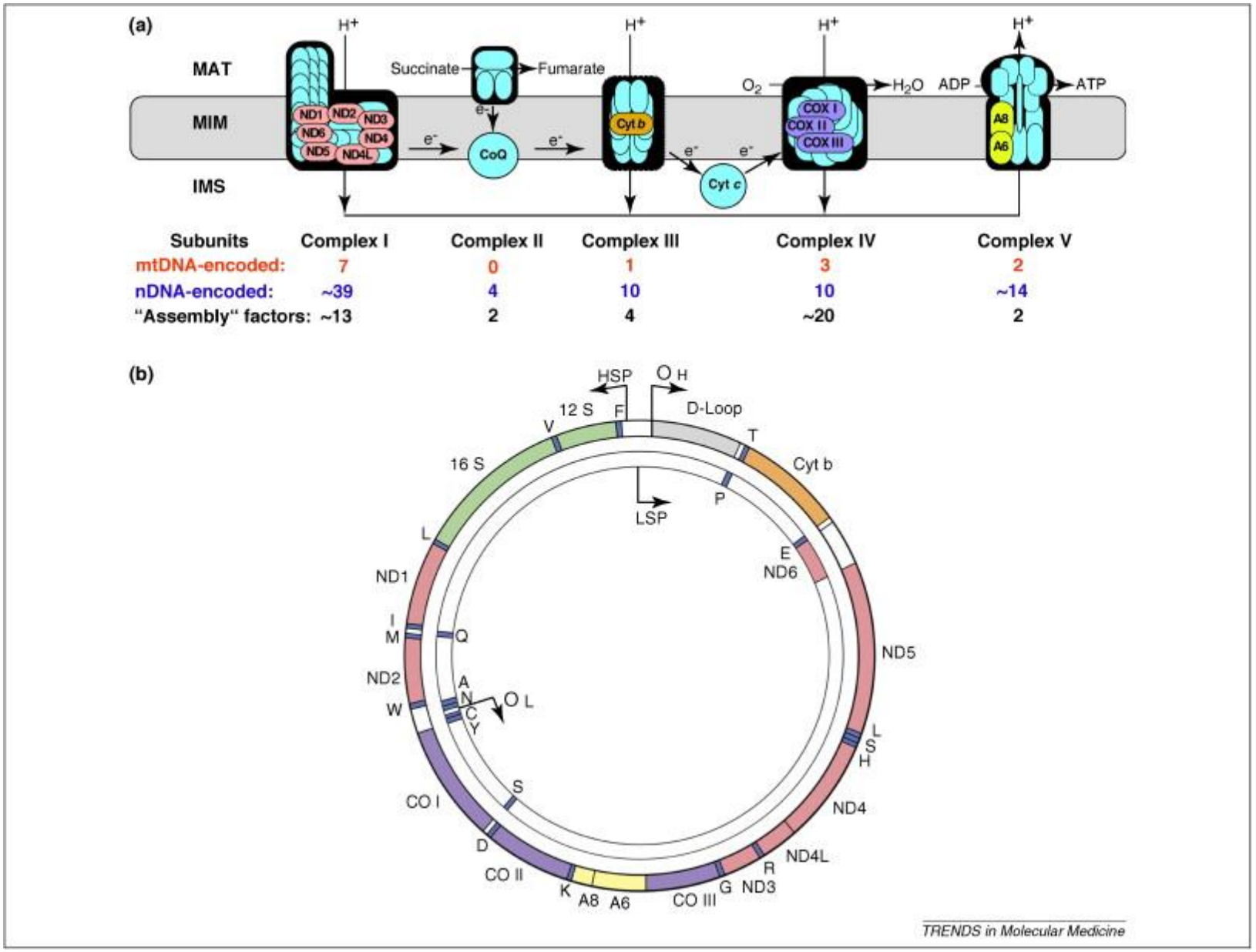
Communicated by Britton Chance, August 29, 1966

of the last few years have demonstrated that a small amount c
cifically in one or more central regions of mitochondria[1–4] represe
vertebrate and invertebrate phyla.[4] A DNA differing in composi
olic[6, 8, 9] properties from nuclear DNA can be isolated from puri
f many organisms. A rapidly expanding body of literature, al

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



Respiratory chain and ATP synthase (OXPHOS)



Journal of Clinical Investigation
Vol. 41, No. 9, 1962

A CASE OF SEVERE HYPERMETABOLISM OF NONTHYROID ORIGIN WITH A DEFECT IN THE MAINTENANCE OF MITOCHONDRIAL RESPIRATORY CONTROL: A CORRELATED CLINICAL, BIOCHEMICAL, AND MORPHOLOGICAL STUDY

By ROLF LUFT,* DENIS IKKOS,* GENARO PALMIERI,* LARS ERNSTER† AND BJÖRN AFZELIUS‡

(From the Department of Endocrinology and Metabolism, Karolinska Sjukhuset, and the Departments of Physiological Chemistry and Biophysics, Wenner-Gren Institute, University of Stockholm, Sweden)

Proc. Natl. Acad. Sci. USA
Vol. 77, No. 11, pp. 6715–6719, November 1980
Genetics

Maternal inheritance of human mitochondrial DNA

(genetic polymorphism/restriction endonuclease cleavage map/blood platelets)

RICHARD E. GILES*†, HUGUES BLANC*, HOWARD M. CANN*‡, AND DOUGLAS C. WALLACE*§

*Department of Genetics and ‡Department of Pediatrics, Stanford University Medical School, Stanford, California 94305

Communicated by L. L. Cavalli-Sforza, July 28, 1980

Nature Vol. 290 9 April 1981

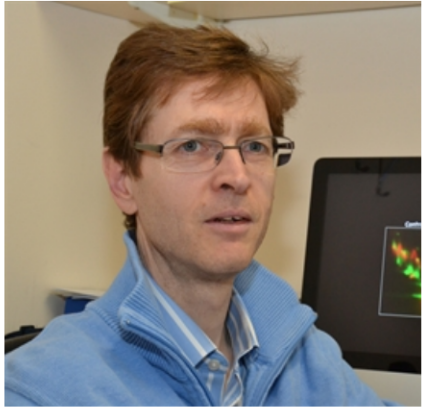
Sequence and organization of the human mitochondrial genome

S. Anderson, A. T. Bankier, B. G. Barrell, M. H. L. de Bruijn, A. R. Coulson, J. Drouin*, I. C. Eperon, D. P. Nierlich*, B. A. Roe*, F. Sanger, P. H. Schreier*, A. J. H. Smith, R. Staden & I. G. Young*

MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, UK

The complete sequence of the 16,569-base pair human mitochondrial genome is presented. The genes for the 12S and 16S rRNAs, 22 tRNAs, cytochrome c oxidase subunits I, II and III, ATPase subunit 6, cytochrome b and eight other predicted protein coding genes have been located. The sequence shows extreme economy in that the genes have none or only a few noncoding bases between them, and in many cases the termination codons are not coded in the DNA but are created post-transcriptionally by polyadenylation of the mRNAs.

1988 – 1995 Mitochondrial Medicine starts



Science, Vol. 242, No. 4884 (Dec. 9, 1988), pp. 1427-1430

Mitochondrial DNA Mutation Associated with Leber's Hereditary Optic Neuropathy

DOUGLAS C. WALLACE,* GURPARKASH SINGH, MARIE T. LOTT, JUDY A. HODGE, THEODORE G. SCHURR, ANGELA M. S. LEZZA, LOUIS J. ELSAS II, EEVA K. NIKOSKELAINEN

Leber's hereditary optic neuropathy is a maternally inherited disease resulting in optic nerve degeneration and cardiac dysrhythmia. A mitochondrial DNA replacement mutation was identified that correlated with this disease in multiple families. This mutation converted a highly conserved arginine to a histidine at codon 340 in the NADH dehydrogenase subunit 4 gene and eliminated an Sfa NI site, thus providing a simple diagnostic test. This finding demonstrated that a nucleotide change in a mitochondrial DNA energy production gene can result in a neurological disease.

NATURE VOL. 331 25 FEBRUARY 1988

Deletions of muscle mitochondrial DNA in patients with mitochondrial myopathies

I. J. Holt, A. E. Harding & J. A. Morgan-Hughes

Department of Clinical Neurology, Institute of Neurology, Queen Square, London WC1N 3BG, UK

***In vitro* studies of muscle mitochondrial metabolism in patients with mitochondrial myopathy have identified a variety of functional defects of the mitochondrial respiratory chain, predominantly affecting complex I (NADH-CoQ reductase) or complex III (ubiquinol–cytochrome *c* reductase) in adult cases[1–3]. These two enzymes consist of ~36 subunits, eight of which are encoded by mitochondrial DNA (mtDNA)[4–6]. The increased incidence of maternal, as opposed to paternal, transmission in familial mitochondrial myopathy suggests that these disorders may be caused by mutations of mtDNA[7,8]. Multiple restriction endonuclease analysis of leukocyte mtDNA from patients with the disease, and their relatives, showed no differences in cleavage patterns between affected and unaffected individuals in any single maternal line. When muscle mtDNA was studied, nine of 25 patients were found to have two populations of muscle mtDNA, one of which had deletions of up to 7 kilobases in length. These observations demonstrate that mtDNA heteroplasmy can occur in man and that human disease may be associated with defects of the mitochondrial genome.**

Nature Genetics volume 11 october 1995

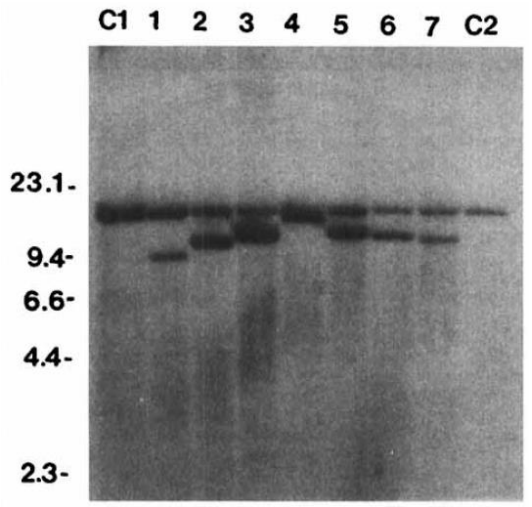
Mutation of a nuclear succinate dehydrogenase gene results in mitochondrial respiratory chain deficiency

Thomas Bourgeron, Pierre Rustin, Dominique Chretien, Mark Birch-Machin, Marie Bourgeois, Evani Viegas-Péquignot[1], Arnold Munnich & Agnès Rötig

NEUROLOGY 1988;38:1339-1346

Deletions of mitochondrial DNA in Kearns-Sayre syndrome

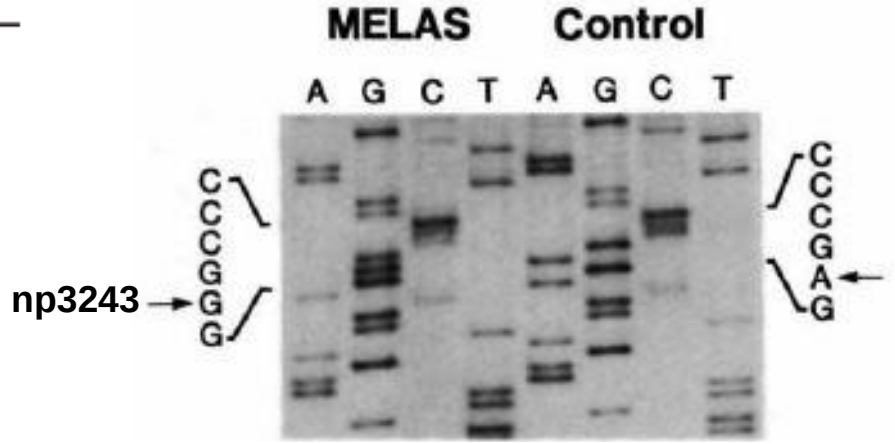
M. Zeviani, MD; C.T. Moraes, MSc; S. DiMauro, MD; H. Nakase, MD; E. Bonilla, MD; E.A. Schon, PhD; and L.P. Rowland, MD



NATURE · VOL 348 · 13 DECEMBER 1990

A mutation in the tRNA$^{Leu(UUR)}$ gene associated with the MELAS subgroup of mitochondrial encephalomyopathies

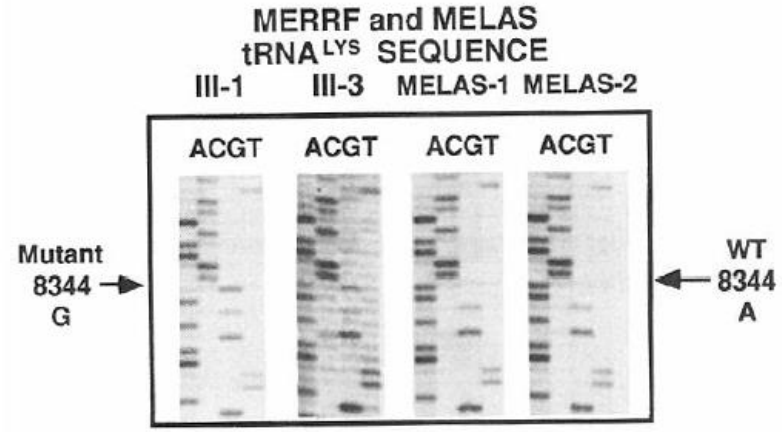
Yu-ichi Goto*†, Ikuya Nonaka* & Satoshi Horai‡§



Cell, Vol. 61, 931–937, June 15, 1990, Copyright © 1990 by Cell Press

Myoclonic Epilepsy and Ragged-Red Fib Disease (MERRF) Is Associated with a Mitochondrial DNA tRNA^{Lys} Mutation

John M. Shoffner,* Marie T. Lott,†
Angela M. S. Lezza,†‡ Peter Seibel,†§
Scott W. Ballinger,† and Douglas C. Wallace*†‖



MELAS syndrome:
Characteristic migrainous and epileptic features and maternal transmission

P. Montagna, MD; R. Gallassi, MD; R. Medori, MD; E. Govoni, MD; M. Zeviani, MD; S. Di Mauro, MD; E. Lugaresi, MD; and F. Andermann, MD

Article abstract—Severe prolonged migrainous symptoms and prolonged partial status epilepticus are characteristic features of the MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes). Maternal transmission previously found in myoclonus epilepsy and ragged-red fibers (MERRF), another mitochondrial disease, is suggested in this disorder as well.

NEUROLOGY 1988;38:751-754

Prime descrizioni di pazienti italiani con le malattie mitocondriali MELAS, LHON e NARP

Leber's hereditary optic neuropathy:
Genetic, biochemical, and phosphorus magnetic resonance spectroscopy study in an Italian family

P. Cortelli, MD; P. Montagna, MD; P. Avoni, MD; S. Sangiorgi, MD; N. Bresolin, MD; M. Moggio, MD; P. Zaniol, PhD; V. Mantovani, MD; P. Barboni, MD; B. Barbiroli, MD; and E. Lugaresi, MD

Article abstract—Three siblings of a family affected with Leber's hereditary optic neuropathy (LHON) showed a mitochondrial DNA mutation at position 11778. The lactate response to a standardized effort was increased in only one case. Muscle biopsies and biochemistry of muscle and platelet mitochondrial enzymes were normal. All patients showed an altered energy metabolism during exercise and during recovery after exercise on phosphorus 31-magnetic resonance spectroscopy (^{31}P-MRS) of muscle. Brain ^{31}P-MRS showed a decreased energy reserve (decreased PCr/Pi ratio) in all patients. ^{31}P-MRS noninvasively demonstrated an altered mitochondrial energy metabolism in muscle and, for the first time, in the brains of LHON patients.

NEUROLOGY 1991;41:1211-1215

British Journal of Ophthalmology 1993; 77: 84–88

Retinitis pigmentosa, ataxia, and mental retardation associated with mitochondrial DNA mutation in an Italian family

Piero Puddu, Piero Barboni, Vilma Mantovani, Pasquale Montagna, Angelina Cerullo, Michela Bragliani, Carla Molinotti, Roberto Caramazza

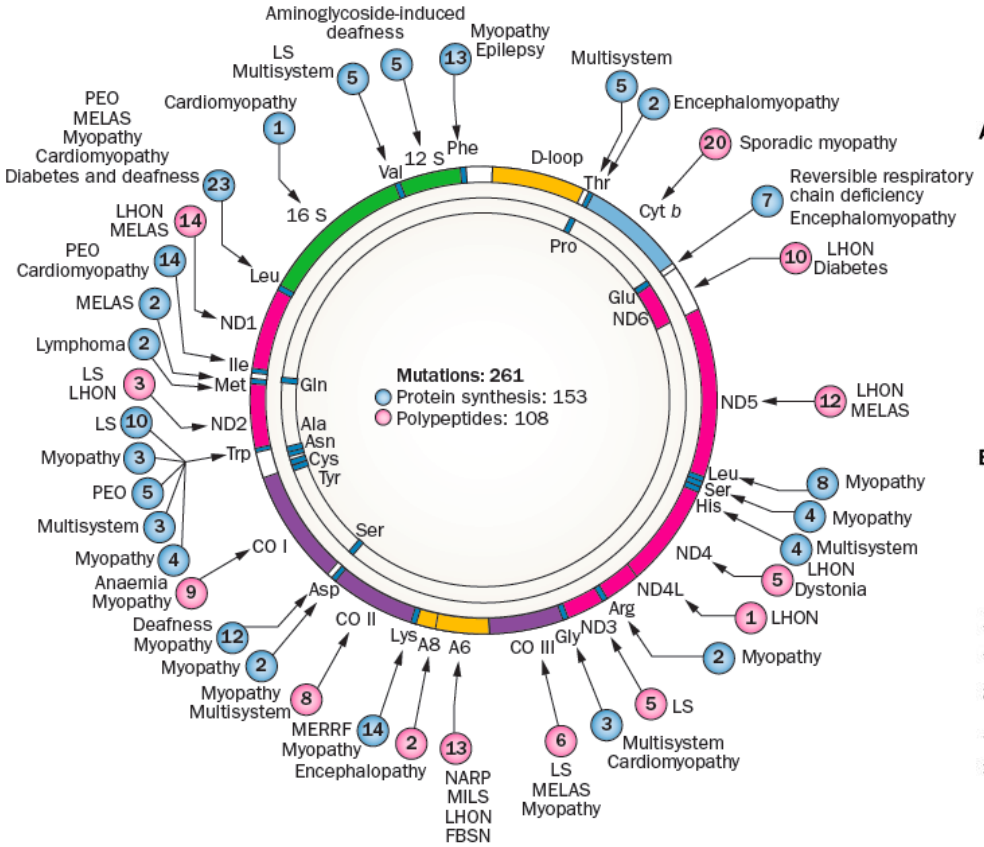
Essays in Biochemistry (2016) **62** 235–254
https://doi.org/10.1042/EBC20170097

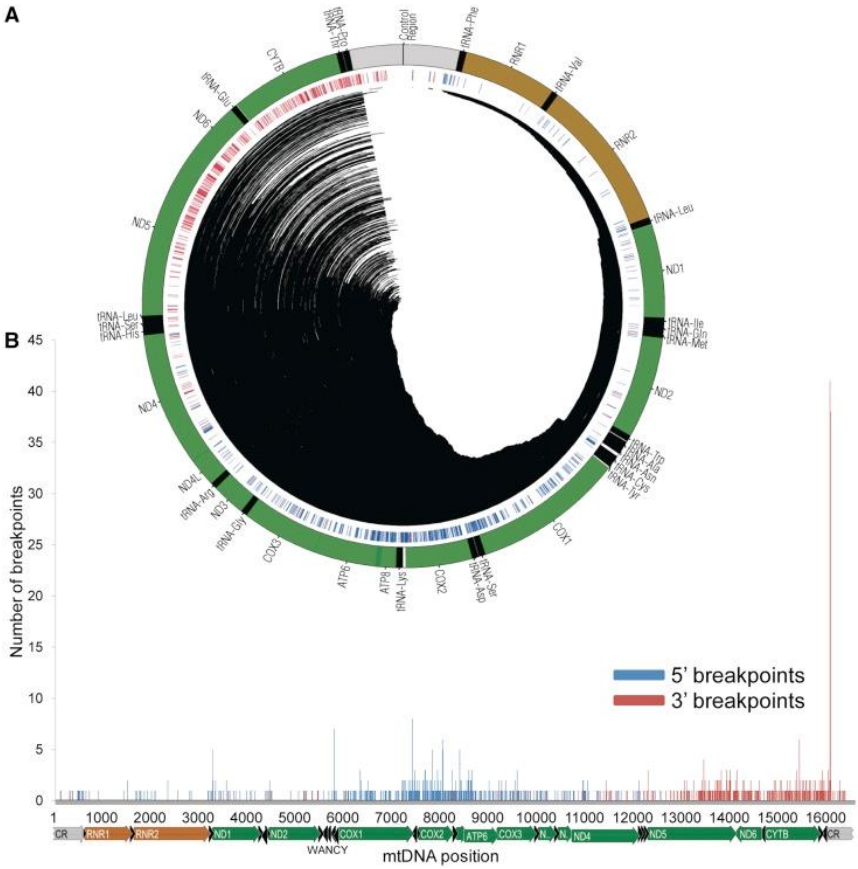
PORTLAND PRESS

Review Article

Clinical syndromes associated with mtDNA mutations: where we stand after 30 years

Valerio Carelli[1,2] and Chiara La Morgia[1,2]





REVIEWS
NATURE REVIEWS | NEUROLOGY

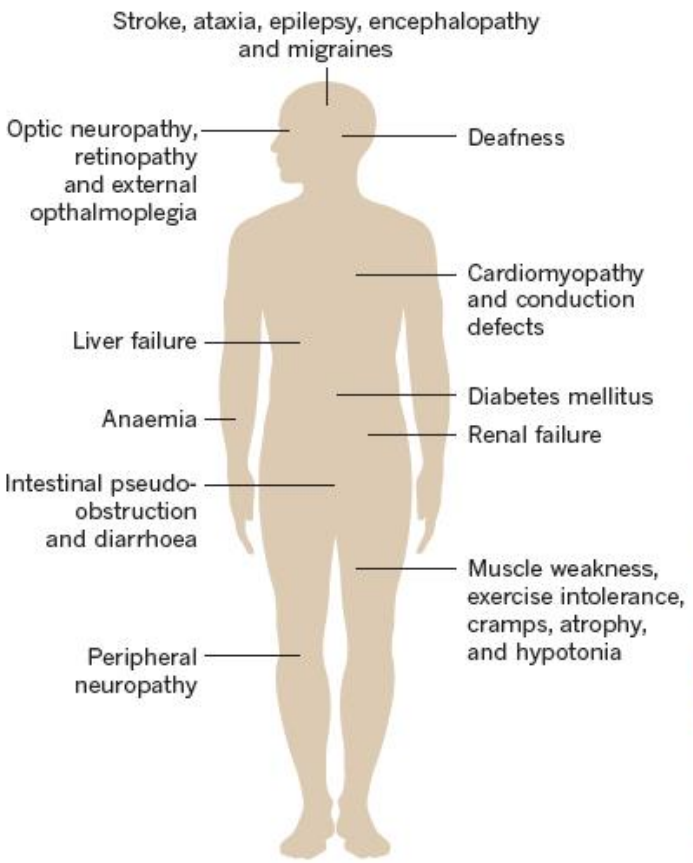
The clinical maze of mitochondrial neurology

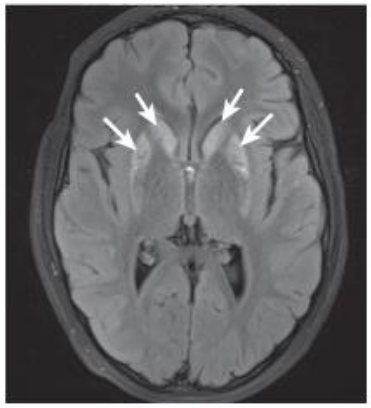
Salvatore DiMauro, Eric A. Schon, Valerio Carelli and Michio Hirano

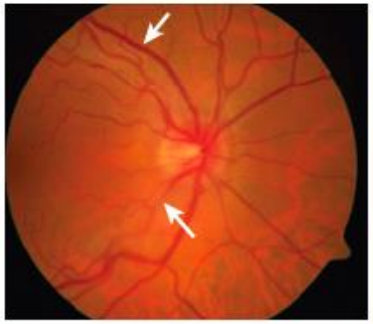
Mitochondrial disorders in neurology are either underdiagnosed ("what is this bizarre syndrome?") or overdiagnosed ("this syndrome is so bizarre that it must be mitochondrial").

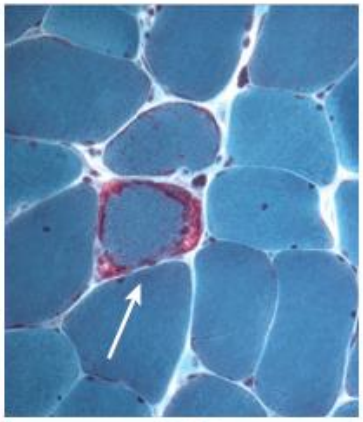
Salvatore Di Mauro 2013

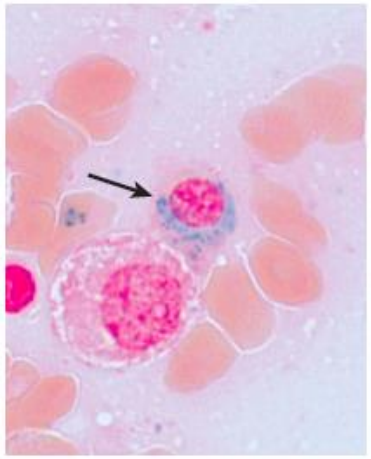
1988 – 2018
30 years of Mitochondrial Medicine

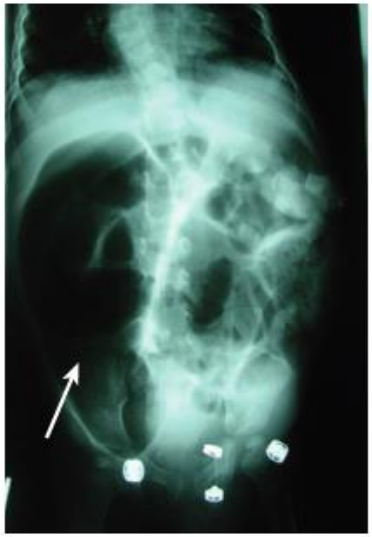


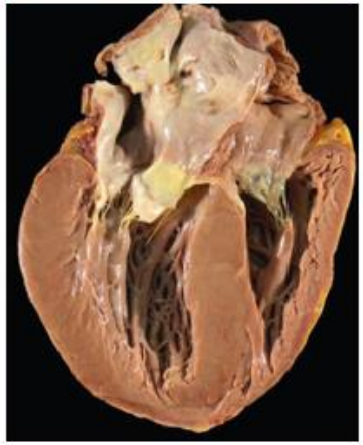




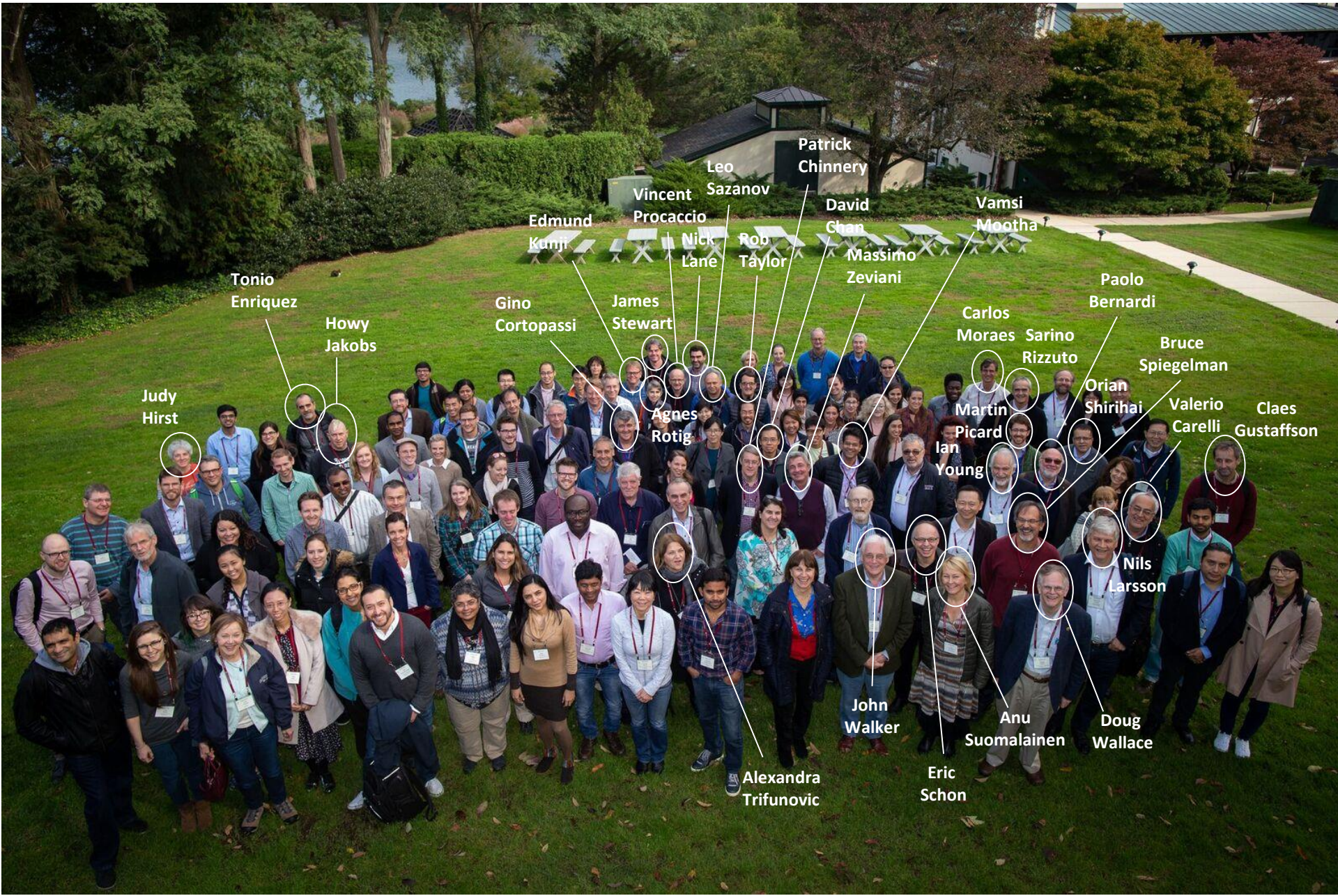








Historical meeting on mitochondrial genetics in Cold Spring Harbor Laboratory 2018



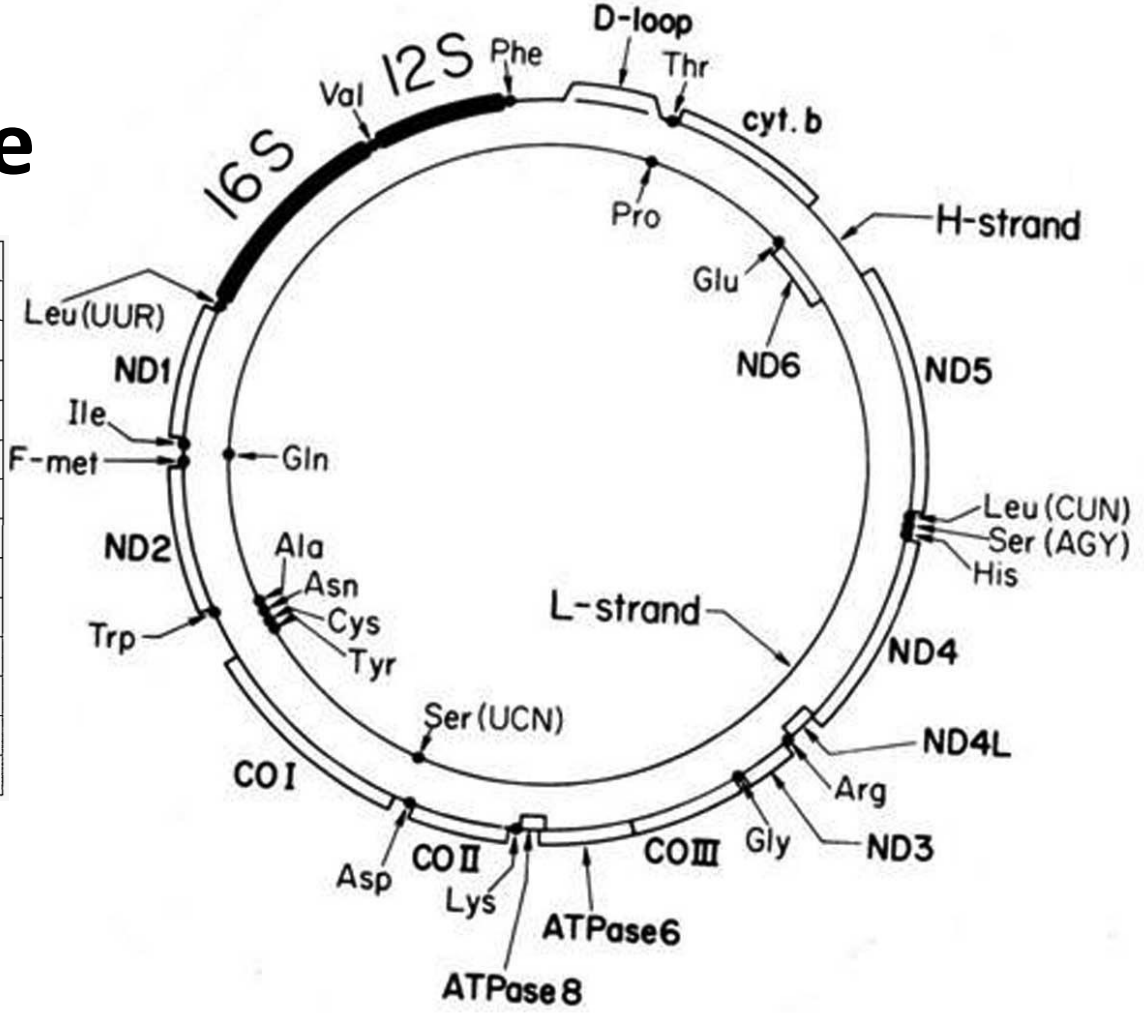
Different genetic code

RNA Codon	Nuclear Genetic Code	mtDNA Genetic Code		
		Mammals	Drosophila	Yeasts
UGA	STOP	Tryptophan	Tryptophan	Tryptophan
AGA, AGG	Arginine	STOP	Serine	Arginine
AUA	Isoleucine	Methionine	Methionine	Methionine
AUU	Isoleucine	Methionine	Methionine	Methionine
CUU, CUC, CUA, CUG	Leucine	Leucine	Leucine	Threonine

MtDNA is the only source of critical cellular proteins outside of the eukaryotic nucleus. In the majority of eukaryotes, mtDNA is organizsed as a circular, double-stranded DNA molecule (Fig. 1).[5] The strands are distinguished by their nucleotide composition: heavy (H-strand) is guanine rich, compared with the cytosine-rich light strand (L-strand). The length varies between species (15 000–17 000 bp), but is fairly consistent in humans (~16 569 bp).[5] MtDNA is a multi-copy DNA, with cells containing between 100 and 10 000 copies of mtDNA (dependent upon cellular energy demand).

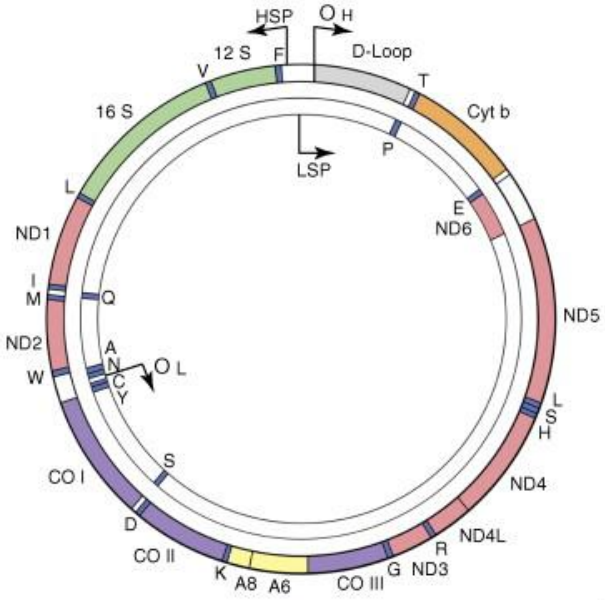
mtDNA structure

Gene	Map Locus[a]	Abbreviation	Location[b]
NADH dehydrogenase 1	MTND1	ND1	3307-4262
NADH dehydrogenase 2	MTND2	ND2	4470-5511
NADH dehydrogenase 3	MTND3	ND3	10059-10404
NADH dehydrogenase 4L	MTND4L	ND4L	10470-10766
NADH dehydrogenase 4	MTND4	ND4	10760-12137
NADH dehydrogenase 5	MTND5	ND5	12337-14148
NADH dehydrogenase 6	MTND6	ND6	14149-14673
Cytochrome b	MTCYB	Cytb	14747-15887
Cytochrome c oxidase I	MTCO1	COI	5904-7445
Cytochrome c oxidase II	MTCO2	COII	7586-8269
Cytochrome c oxidase III	MTCO3	COIII	9207-9990
ATP synthase 6	MTATP6	ATP6	8527-9207
ATP synthase 8	MTATP8	ATP8	8366-8572



…and

22 tRNAs plus 2 rRNAs



Opinion TRENDS in Biochemical Sciences Vol.28 No.7 July 2003 357

The mitochondrial DNA replication bubble has not burst

Daniel F. Bogenhagen[1] and David A. Clayton[2]

[1]Department of Pharmacology, State University of New York at Stony Brook, Stony Brook, NY 11794, USA
[2]Howard Hughes Medical Institute, 4000 Jones Bridge Road, Chevy Chase, MD 20815, USA

Response: The mitochondrial DNA replication bubble has not burst☆

Ian J. Holt[1] and Howard T. Jacobs[2]

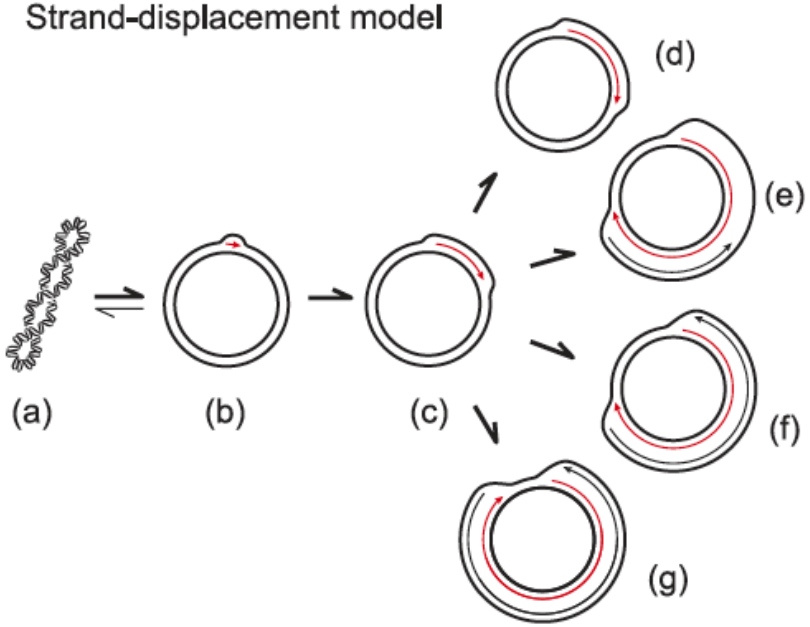
[1]MRC-Dunn Human Nutrition Unit, Hills Road, Cambridge, UK CB2 2XY
[2]Institute of Medical Technology and Tampere University Hospital, University of Tampere, Finland, FIN-33014

Concluding remarks: The mitochondrial DNA replication bubble has not burst

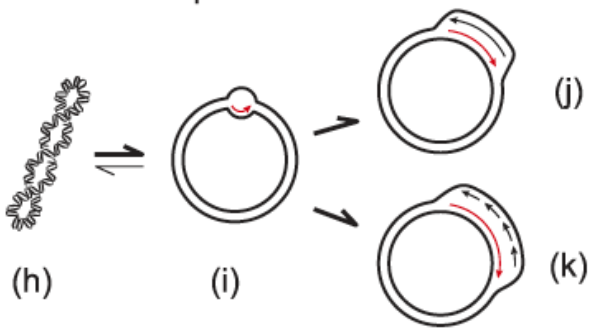
Daniel F. Bogenhagen[1] and David A. Clayton[2]

[1]Department of Pharmacology, State University of New York at Stony Brook, Stony Brook, NY 11794, USA
[2]Howard Hughes Medical Institute, 4000 Jones Bridge Road, Chevy Chase, MD 20815, USA

Strand-displacement model



Strand-coupled model



mtDNA REPLISOME

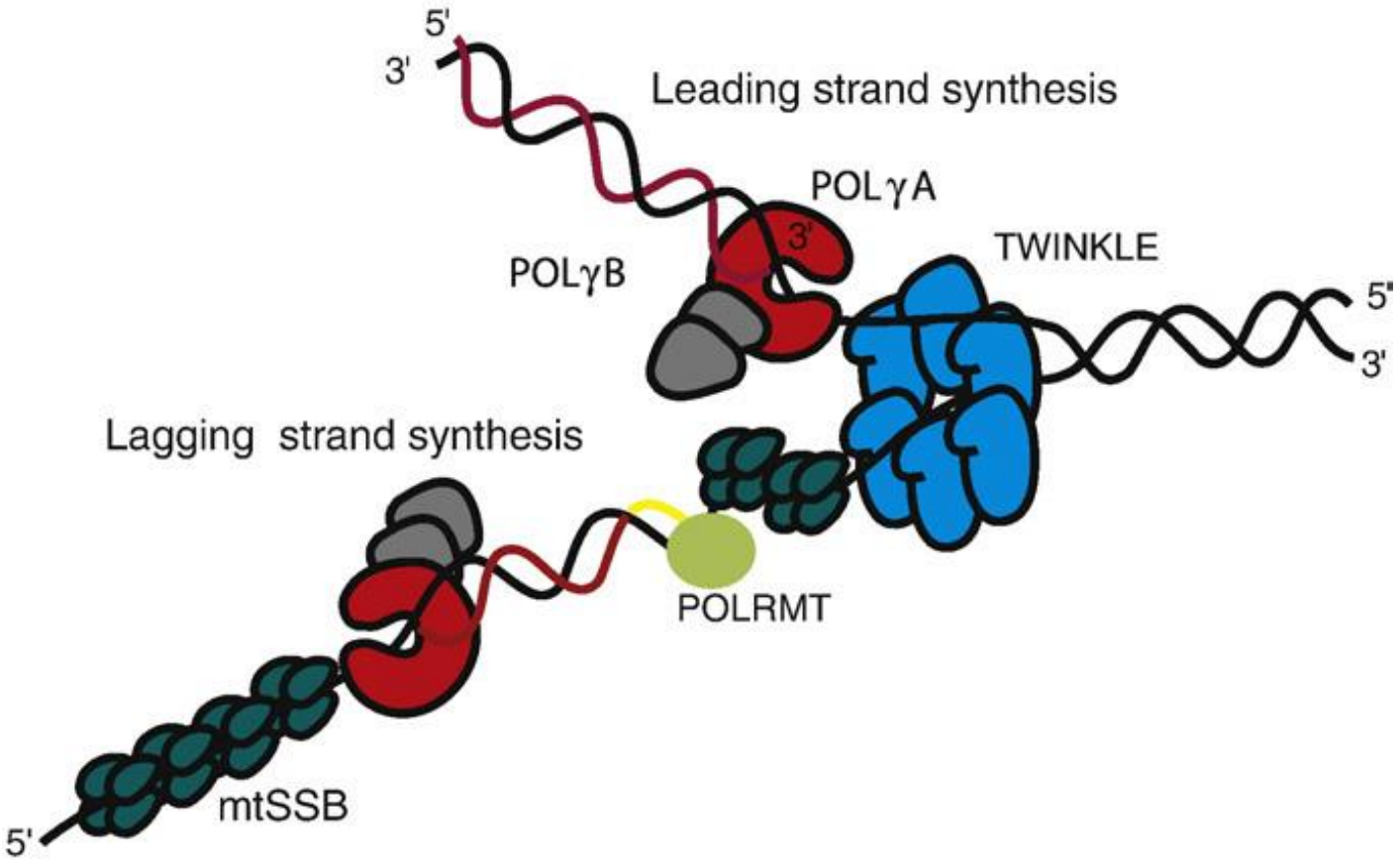


Fig. 2. The mtDNA replication machinery. The TWINKLE helicase (blue) moves in a 5' to 3' direction while unwinding dsDNA. The mtSSB protein (dark green) stabilizes the single stranded conformation and stimulates the DNA synthesis by the POLγ (red (A) and gray (B)). POLRMT (light green) synthesizes the RNA primer (yellow line) needed for lagging strand DNA synthesis.

Super-resolution microscopy reveals that mammalian mitochondrial nucleoids have a uniform size and frequently contain a single copy of mtDNA

Christian Kukat[a,1], Christian A. Wurm[b,c,1], Henrik Spåhr[a], Maria Falkenberg[d], Nils-Göran Larsson[a,2], and Stefan Jakobs[b,c,2]

[a]Department of Mitochondrial Biology, Max Planck Institute for Biology of Ageing, D-50931 Cologne, Germany; [b]Department of NanoBiophotonics, Mitochondrial Structure and Dynamics Group, Max Planck Institute for Biophysical Chemistry, and [c]Department of Neurology, University of Göttingen, D-37077 Göttingen, Germany; and [d]Department of Medical Biochemistry and Cell Biology, University of Gothenburg; SE-40530 Gothenburg, Sweden

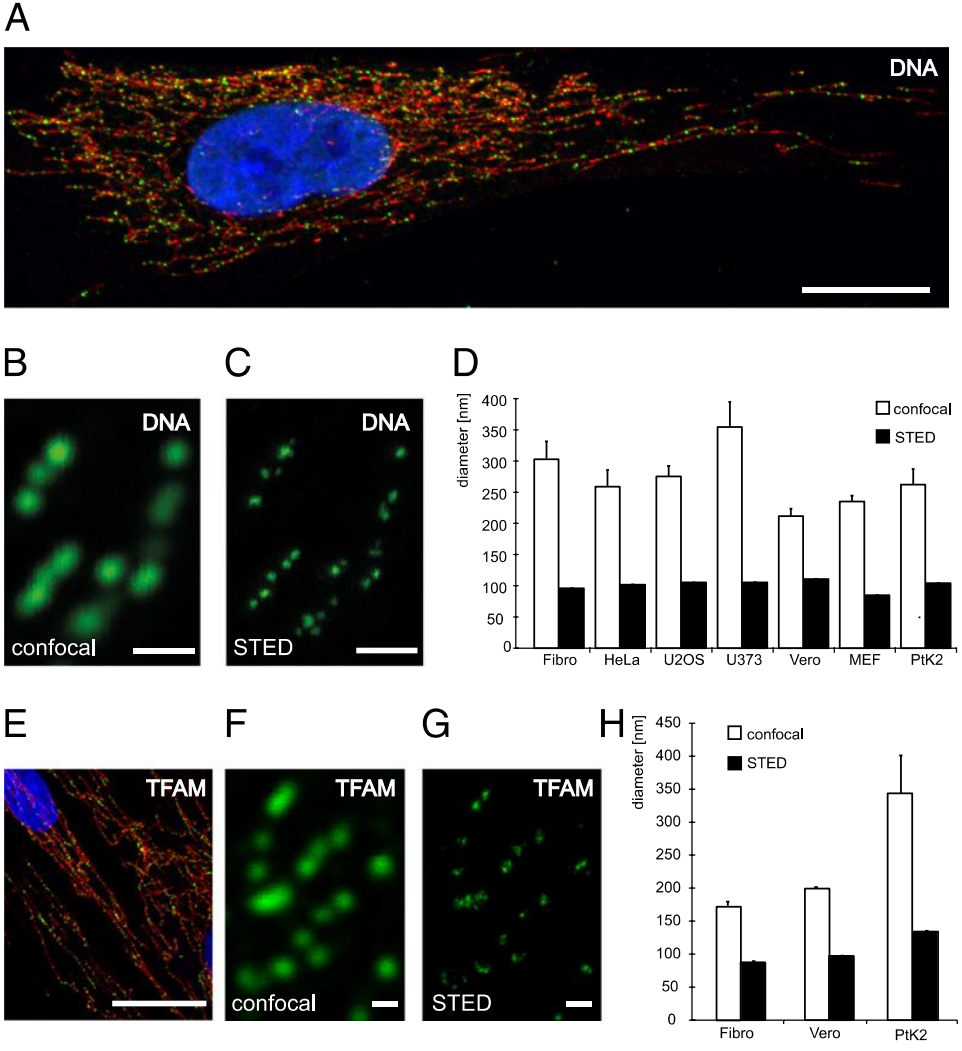


Fig. 1. The nucleoid has a uniform mean size in mammalian cells. (*A*) mtDNA (green, DNA antibodies) is localized in nucleoids in the tubular mitochondria (red, anti-TOM20) of human fibroblasts. DAPI-staining of nucleus in blue. (*B*) Using confocal microscopy, nucleoids labeled with an antiserum against DNA appear to be solid structures with an average diameter of ~300 nm in human fibroblasts. (*C*) Applying super-resolution STED microscopy, we found that the apparent nucleoids, as detected by confocal microscopy, frequently are agglomerates of several smaller structures, each with an average diameter of ~99 nm. The section shown is the same as the one in *B*. (*D*) Sizes of nucleoids labeled with a DNA antibody determined by confocal and STED imaging in mammalian cell lines, such as, human primary culture fibroblasts (Fibro), human cervix adenocarcinoma cells (HeLa), human osteosarcoma cells (U2OS), human glioblastoma cells (U373), mouse embryonic fibroblasts (MEF), African green monkey kidney epithelial cells (Vero), and potoroo kidney cells (PtK2). The indicated sizes denote the antibody labeled nucleoids. (*E*) TFAM (green, anti-TFAM) is located in nucleoids in the mitochondrial network (red, anti-TOM20) of human fibroblasts. Nuclear DAPI-staining in blue. (*F*) Using confocal microscopy, the nucleoids labeled with an antiserum against TFAM appear in a punctuate pattern. (*G*) STED microscopy reveals a mean diameter of ~88 nm for nucleoids labeled with a TFAM antibody in human fibroblasts. The section shown is the same as the one in *F*. (*H*) Quantification of the sizes of nucleoids labeled with TFAM antibodies determined by confocal and STED imaging in three mammalian cell lines. Error bars indicate SEM. (Scale bars: 20 μm in *A* and *E*, 0.5 μm in *B*, *C*, *F*, and *G*.)

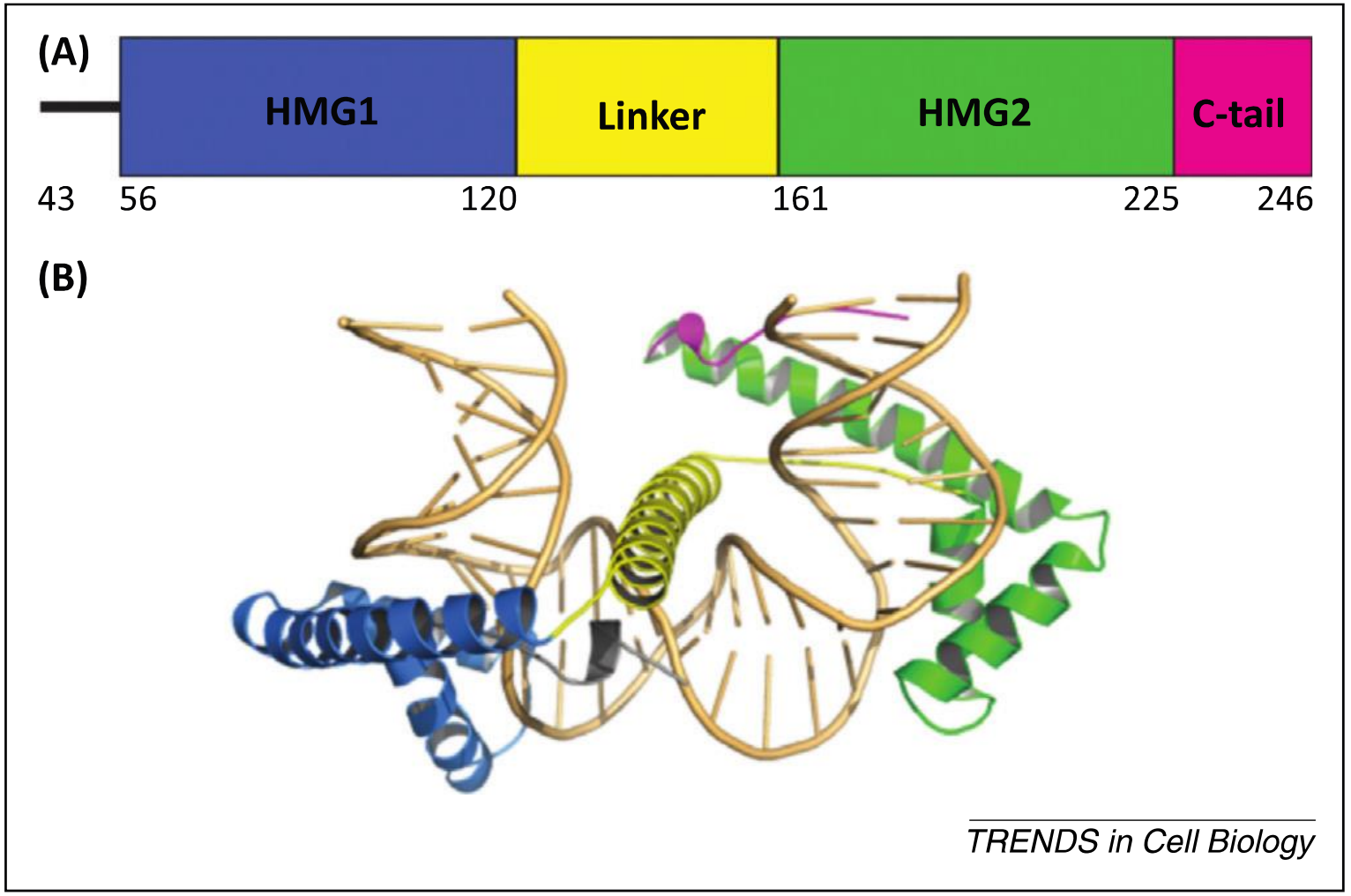
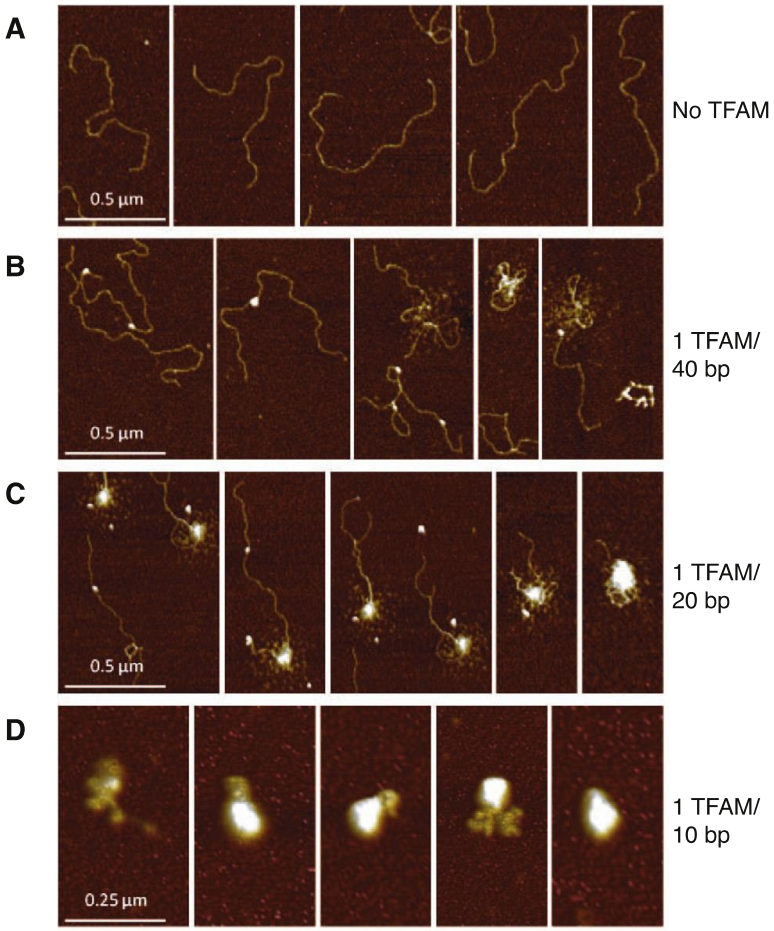
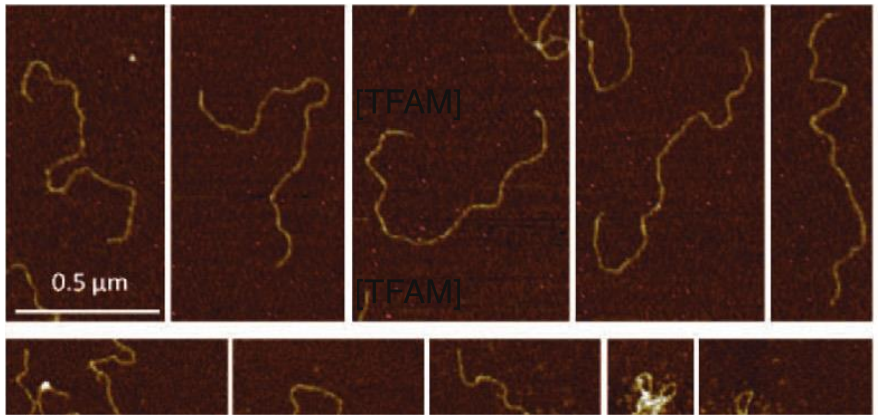


Figure 1. The structure of the mitochondrial transcription factor A (TFAM). **(A)** Domain structure of mature TFAM; numbers indicate amino acids. Amino acids 1–42 form the mitochondrial targeting sequence that is cleaved upon import of TFAM into the mitochondrial matrix. HMG, high mobility group domain; C-tail, C-terminal tail. **(B)** The TFAM–DNA complex. TFAM in complex with 28 bp LSP (light strand promoter) DNA [14] induces a U-turn into the DNA strand. TFAM domains are color-coded as in (A) and DNA is colored in beige.

In Vitro-Reconstituted Nucleoids Can Block Mitochondrial DNA Replication and Transcription

Géraldine Farge,[1,4] Majda Mehmedovic,[2,4] Marian Baclayon,[1] Siet M.J.L. van den Wildenberg,[3] Wouter H. Roos,[1] Claes M. Gustafsson,[2] Gijs J.L. Wuite,[1,5,*] and Maria Falkenberg[2,5,*]





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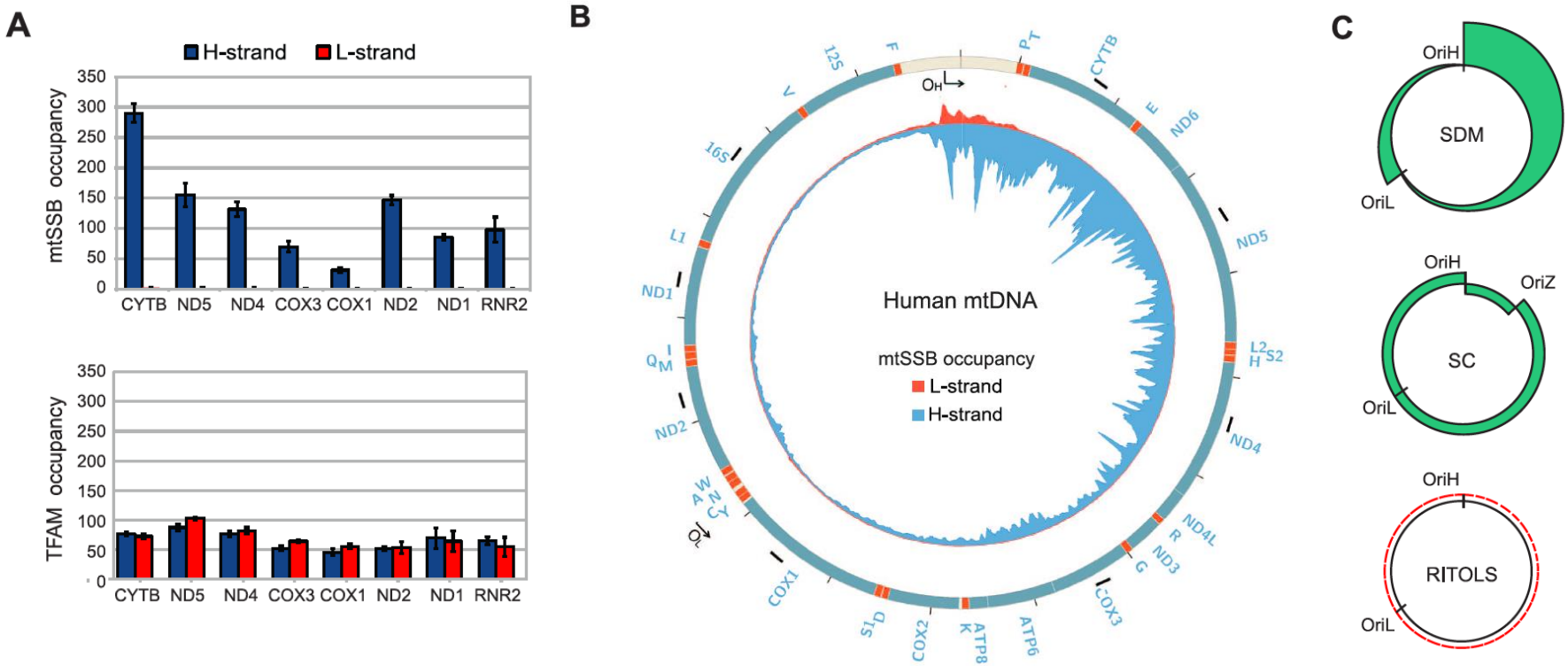
PLOS | GENETICS

In Vivo Occupancy of Mitochondrial Single-Stranded DNA Binding Protein Supports the Strand Displacement Mode of DNA Replication

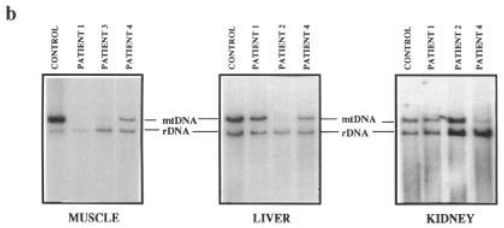
Javier Miralles Fusté[1☯], Yonghong Shi[1☯], Sjoerd Wanrooij[2], Xuefeng Zhu[1], Elisabeth Jemt[1], Örjan Persson[1], Nasim Sabouri[2], Claes M. Gustafsson[1], Maria Falkenberg[1]*



nDNA affects mtDNA:

disorders of mtDNA mantainance (depletion and multiple deletions)

Am. J. Hum. Genet. 48:492–501, 1991



mtDNA Depletion with Variable Tissue Expression: A Novel Genetic Abnormality in Mitochondrial Diseases

Carlos T. Moraes,* Sara Shanske,† Hans-Jürgen Tritschler,† June R. Aprille,‡ Francesca Andreetta,† Eduardo Bonilla,† Eric A. Schon,*'† and Salvatore DiMauro†

Departments of *Genetics and Development and of †Neurology, College of Physicians and Surgeons, Columbia University, New York; and ‡Department of Biology, Tufts University, Medford, MA

Table 2 | Defects of mtDNA maintenance

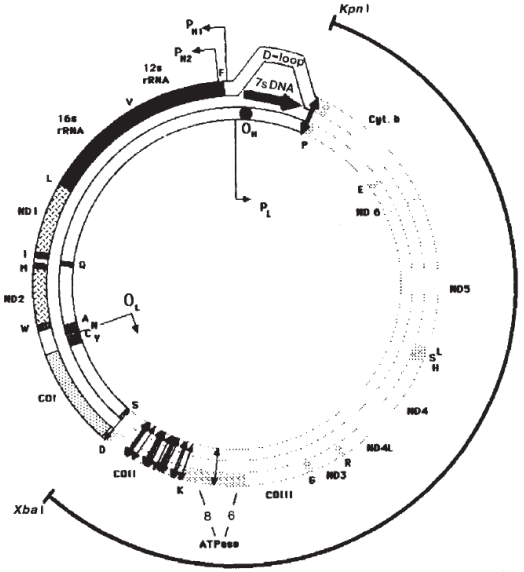
Mutated gene	mtDNA depletion	Multiple mtDNA deletions
TK2	Infantile or adult myopathy SMA phenocopy	Adult autosomal recessive PEO
DGUOK	Infantile hepato-cerebral syndrome	Adult myopathy± PEO
PEO1	Hepato-cerebral syndrome Infantile-onset spinocerebellar ataxia	Adult autosomal dominant PEOplus
SUCLA2	Infantile encephalomyopathy	—
SUCLG1	Infantile encephalomyopathy Methylmalonic aciduria	—
RRM2B	Infantile encephalomyopathy	Adult autosomal dominant or autosomal recessive PEOplus
MPV17	Infantile hepatocerebral syndrome Navajo neurohepatopathy	Adult autosomal recessive PEOplus
TYMP	Mitochondrial neurogastrointestinal encephalomyopathy	Mitochondrial neurogastrointestinal encephalomyopathy
POLG	Hepato-cerebral syndrome (Alpers syndrome)	Adult autosomal dominant or autosomal recessive PEOplus; SANDO; MIRAS
POLG2	—	Adult autosomal dominant PEO
ANT1	—	Adult autosomal dominant PEOplus
OPA1	—	DOA; PEOplus
MFN2	—	DOA-plus
GFER	—	Congenital cataract, encephalomyopathy

Abbreviations: DOA, dominant optic atrophy; MIRAS, mitochondrial recessive ataxia syndrome; mtDNA, mitochondrial DNA; PEO, progressive external ophthalmoplegia; SANDO, sensory ataxic neuropathy, dysarthria and ophthalmoparesis; SMA, spinal muscular atrophy.

NATURE · VOL 339 · 25 MAY 1989

An autosomal dominant disorder with multiple deletions of mitochondrial DNA starting at the D-loop region

Massimo Zeviani*, Serenella Servidei†, Cinzia Gellera*, Enrico Bertini†, Salvatore DiMauro† & Stefano DiDonato*

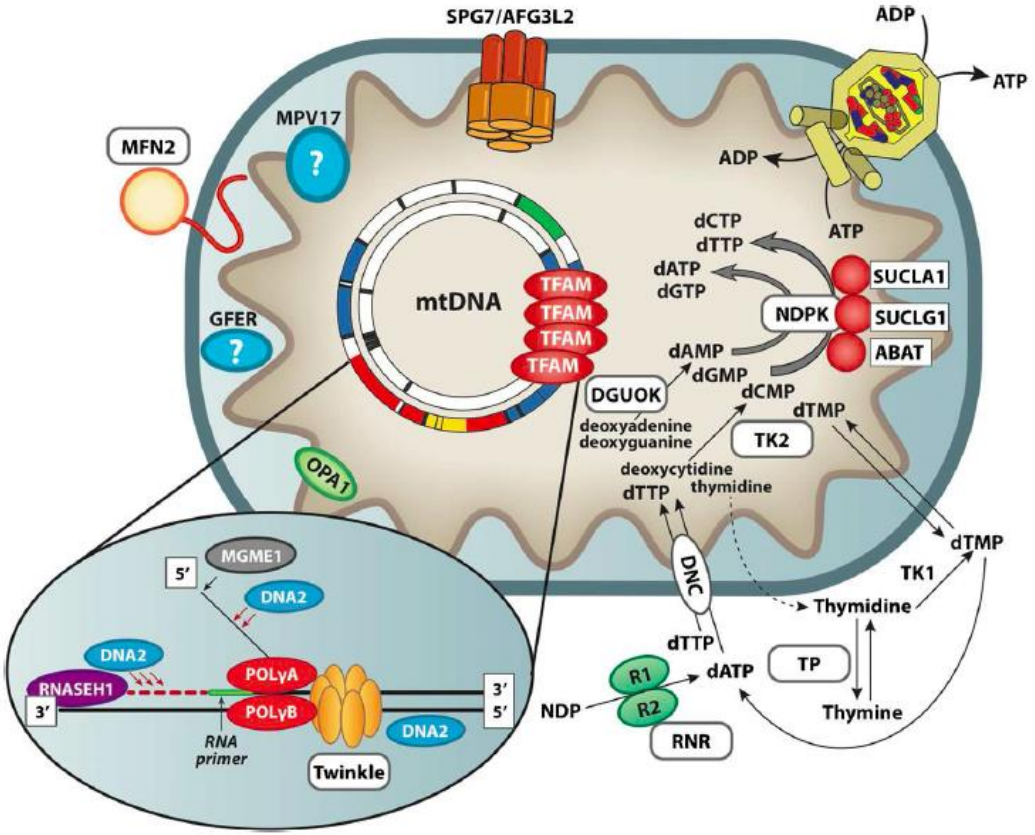


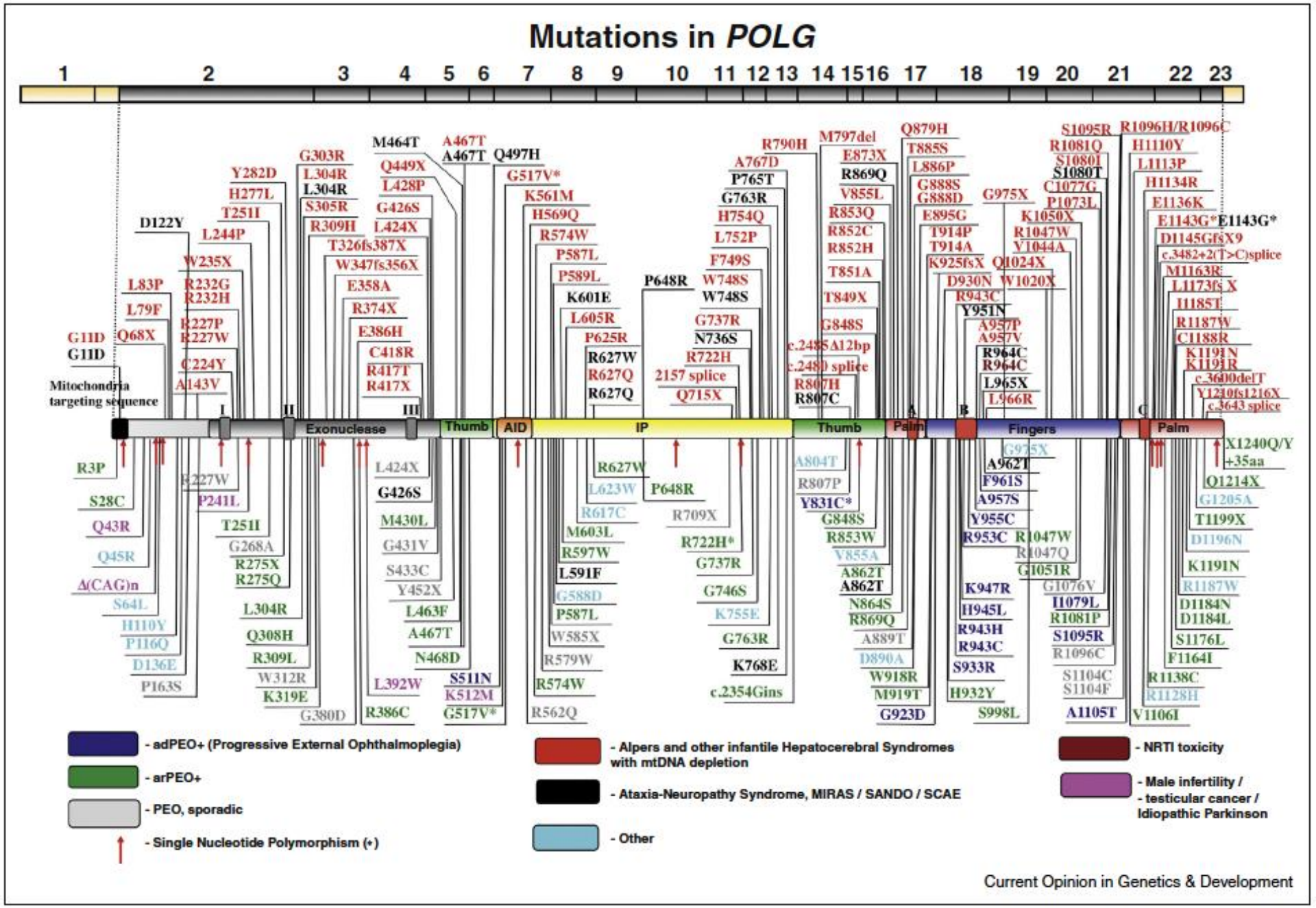
J Inherit Metab Dis (2017) 40:587–599

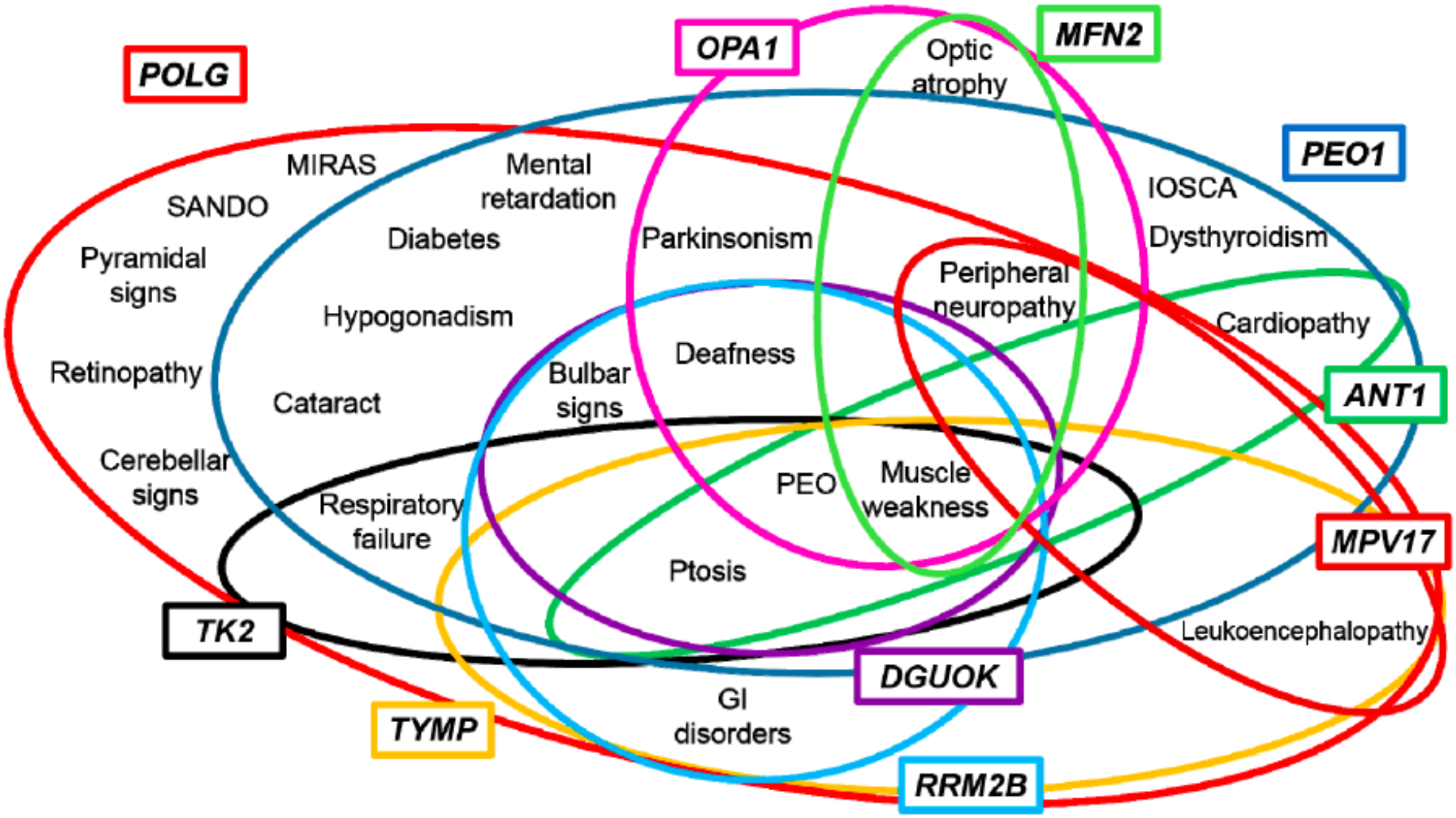
MtDNA-maintenance defects: syndromes and genes

Carlo Viscomi[1] · Massimo Zeviani[1]

Gene	mtDNA alteration	Inheritance	Main clinical phenotype	OMIM
SLC25A4	Multiple deletions	AD	ad/arCPEO	157640/258450
	Multiple deletions	AR	myopathy and cardiomyopathy	615418
	Depletion	AD	myopathy and cardiomyopathy	
TWNK	Multiple deletions	AD	adCPEO	609286
	Multiple deletions	AR	IOSCA	271245
	Depletion	AR	Alpers-like	
POLG	Multiple deletions	AD	adCPEO	157640
	Multiple deletions	AR	arCPEO	258450
	Depletion	AR	Alpers-Huntenlocher	203700
	Multiple deletions	AR	SANDO/SCAE	607459
POLG2	Multiple deletions	AD	adCPEO	610131
TFAM	Depletion	AR	Hepatocerebral syndrome	617156
MGME1	Multiple deletions	AR	arCPEO	615076
DNA2	Multiple deletions	AD	adCPEO	615156
RNASEH1	Multiple deletions	AR	arCPEO	616479
RRM2B	Multiple deletions	AD	adCPEO	613077
	Depletion	AR	myopathy and tubulopathy	612075
TK2	Depletion	AR	myopathy	609560
	Multiple deletions	AR	arCPEO	617069
DGUOK	Depletion	AR	Hepatocerebral syndrome	251880
	Multiple deletions	AR	Myopathy with or w/o CPEO	617070
	Multiple deletions	AR	lower motor neuron syndrome	
MPV17	Depletion	AR	Hepatocerebral syndrome	256810
	Multiple deletions	AR	arCPEO, leukoencephalopathy and parkinsonism	
OPA1	Multiple deletions	AD	DOA	165500
	Multiple deletions	AD	DOA plus	125250
MFN2	Multiple deletions	AD	DOA plus	608507
SPG7	Multiple deletions	AR	arCPEO and ataxia	602783
AFG3L2	Multiple deletions	AD	arCPEO and ataxia	604581
TYMP	Multiple deletions and depletion	AR	MNGIE	603041
SUCLA2	Depletion	AR	Hepatocerebral syndrome	612073
SUCLG1	Depletion	AR	Hepatocerebral syndrome	245400
ABAT	Multiple deletions	AR	Encephalomyopathy	613163
FBXL4	Depletion	AR	Encephalomyopathy	615471
GFER	Multiple deletions	AR	myopathy	613076




Mutations in POLG
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
Mitochondria targeting sequence
I
II
III
Exonuclease
Thumb
AID
IP
Thumb
A
Palm
B
Fingers
C
Palm
- adPEO+ (Progressive External Ophthalmoplegia)
- arPEO+
- PEO, sporadic
- Single Nucleotide Polymorphism (+)
- Alpers and other infantile Hepatocerebral Syndromes with mtDNA depletion
- Ataxia-Neuropathy Syndrome, MIRAS / SANDO / SCAE
- Other
- NRTI toxicity
- Male infertility / - testicular cancer / Idiopathic Parkinson
Current Opinion in Genetics & Development


POLG
OPA1
MFN2
Optic atrophy
PEO1
MIRAS
Mental retardation
SANDO
IOSCA
Diabetes
Parkinsonism
Dysthyroidism
Pyramidal signs
Peripheral neuropathy
Hypogonadism
Cardiopathy
Deafness
Retinopathy
Bulbar signs
ANT1
Cataract
Cerebellar signs
PEO
Muscle weakness
Respiratory failure
MPV17
Ptosis
TK2
Leukoencephalopathy
DGUOK
GI disorders
TYMP
RRM2B

Mitochondrial single strand binding protein 1 (SSBP1):

welcome back!

Gene, 126 (1993) 219–225
 0378-1119/93/$06.00

GENE 07041

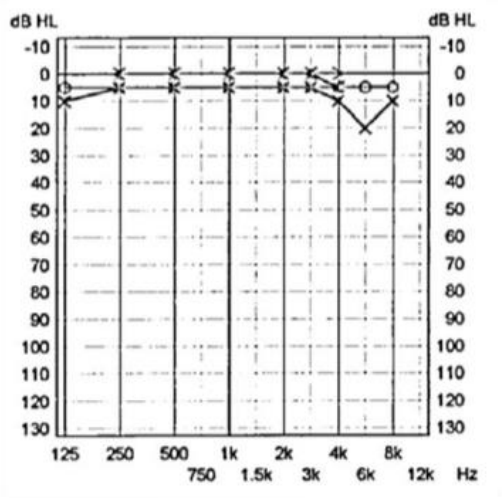
Cloning of human and rat cDNAs encoding the mitochondrial single-stranded DNA-binding protein (SSB)

(Recombinant DNA; nuclear gene; DNA replication; presequence; human chromosome)

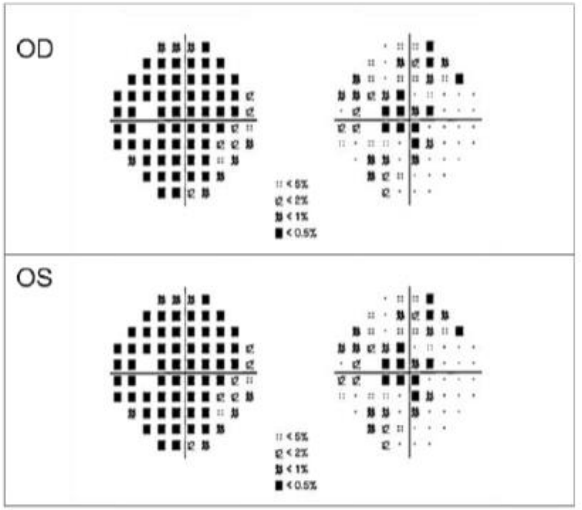
Valeria Tiranti[a], Mariano Rocchi[b], Stefano DiDonato[a] and Massimo Zeviani[a]

Vision defect and sensorineural deafness

K



L



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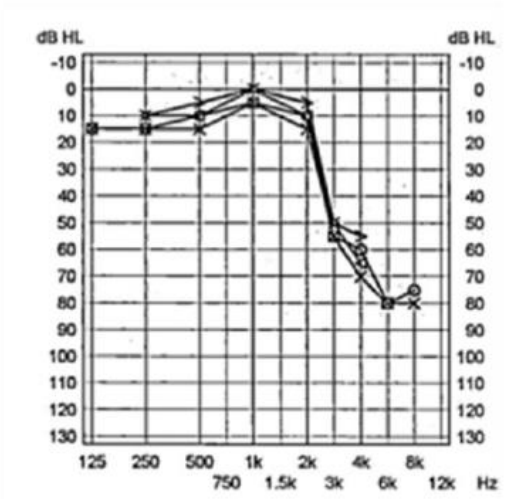

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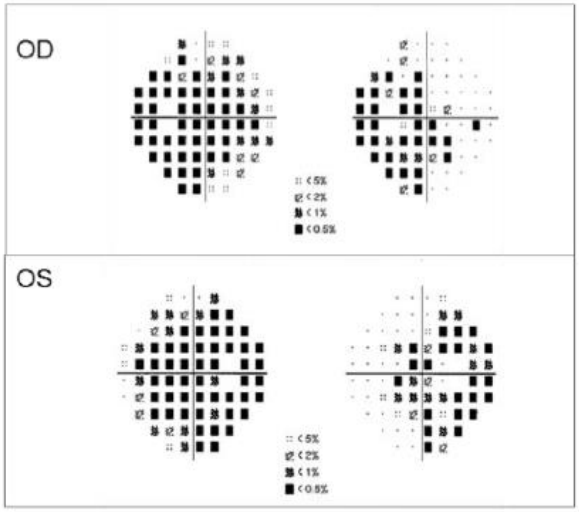
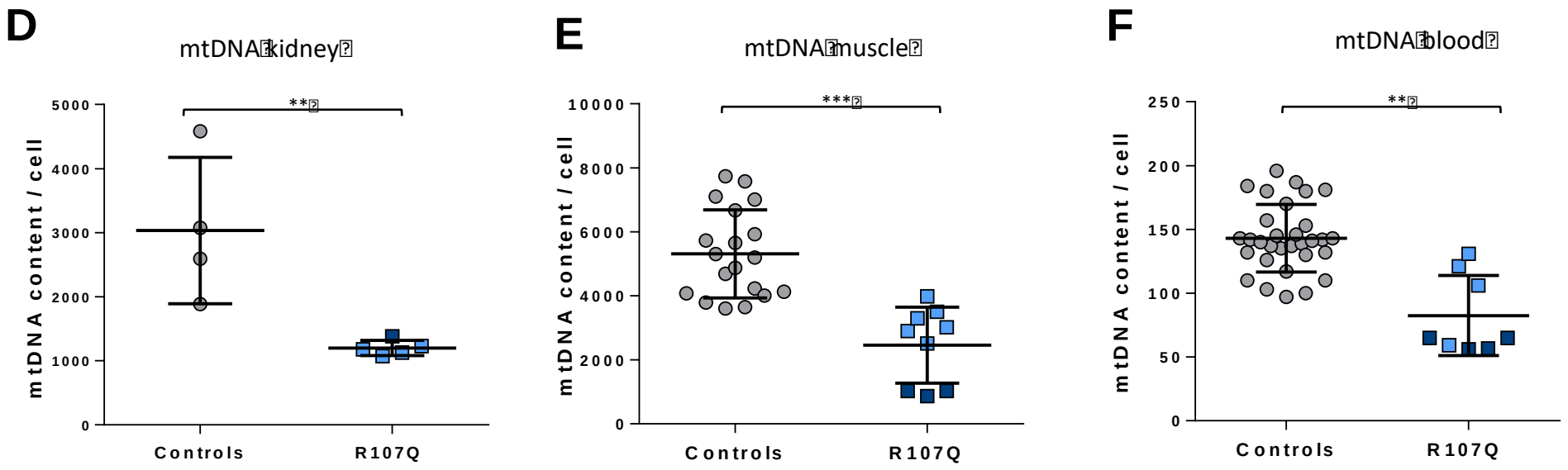
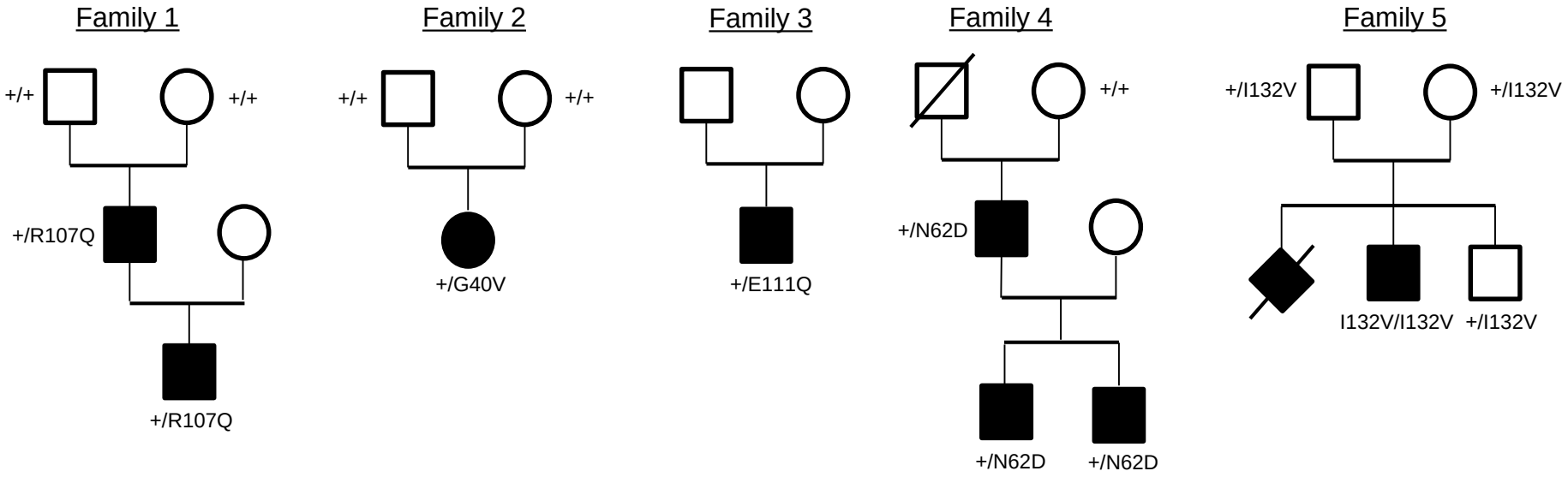


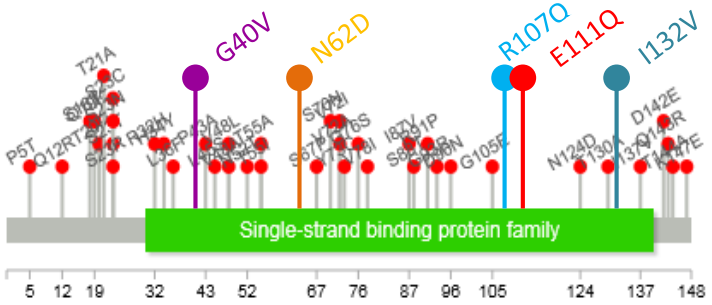
mtDNA depletion in multiple tissues



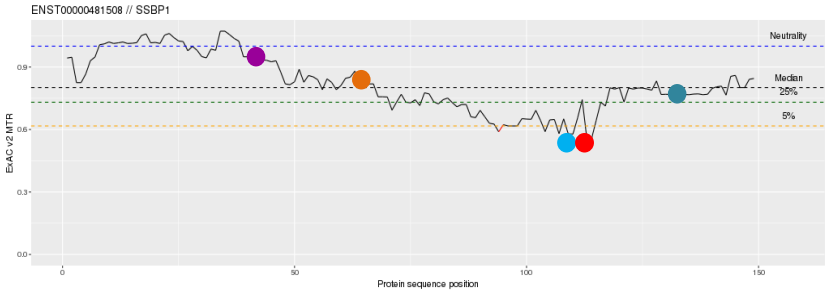
A


Family 1
+/+
+/+
+/R107Q
+/R107Q
Family 2
+/+
+/+
+/G40V
Family 3
+/E111Q
Family 4
+/+
+/N62D
+/N62D
+/N62D
Family 5
+/I132V
+/I132V
I132V/I132V
+/I132V

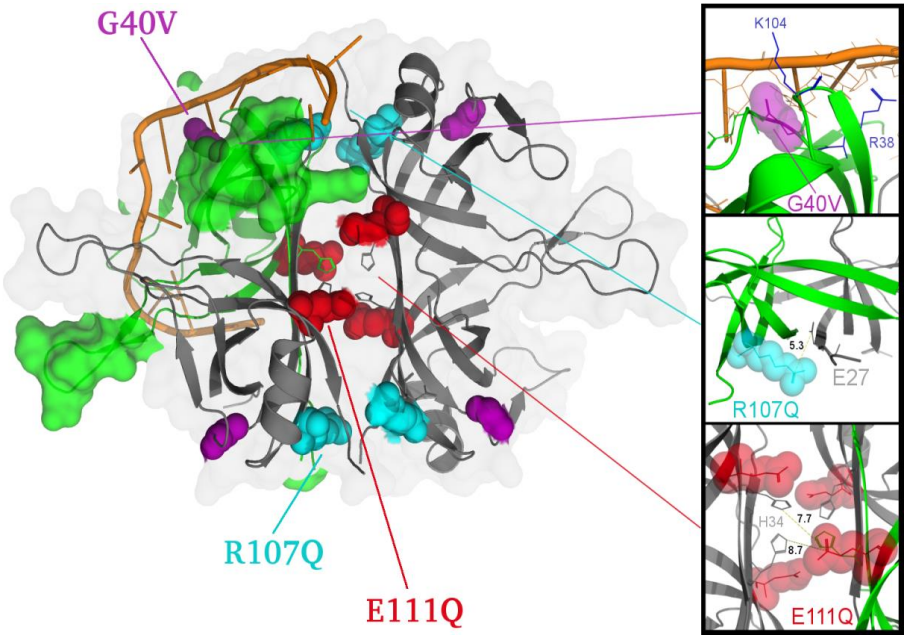
B


G40V
N62D
R107Q
E111Q
I132V
Single-strand binding protein family
5
12
19
32
43
52
67
76
87
96
105
124
137
148

C


ENST00000481508 // SSBP1
Neutrality
Median
25%
5%
EAC v2 MTR
Protein sequence position

D


G40V
R107Q
E111Q
K104
R38
G40V
5.3
E27
R107Q
H34
7.7
8.7
E111Q

CONCLUSIONS

- Unexpectedly, we identified a new disease characterized by mtDNA depletion in adults and associated with a prevalent ocular and kidney phenotype
- Mitochondrial SSBP1 carried dominant de novo pathogenic mutations, and in one case a recessive homozygous mutation
- The current findings enlarge the landscape of diseases of mtDNA maintenance
- In deep dissection of the pathogenic mechanisms will increase our understanding of mtDNA replication and control of mtDNA copy number

Thanks for your attention
and to the many collaborators:

- Valeria Tiranti
- Vania Broccoli
- Holger Prokisch
- Tommaso Pippucci

……and to my lab:

Valentina Del Dotto

Alessandra Maresca

Leonardo Caporali

Francesca Tagliavini

Michele Carbonelli

Chiara La Morgia