Understanding Diseases of Mitochondrial DNA Maintenance

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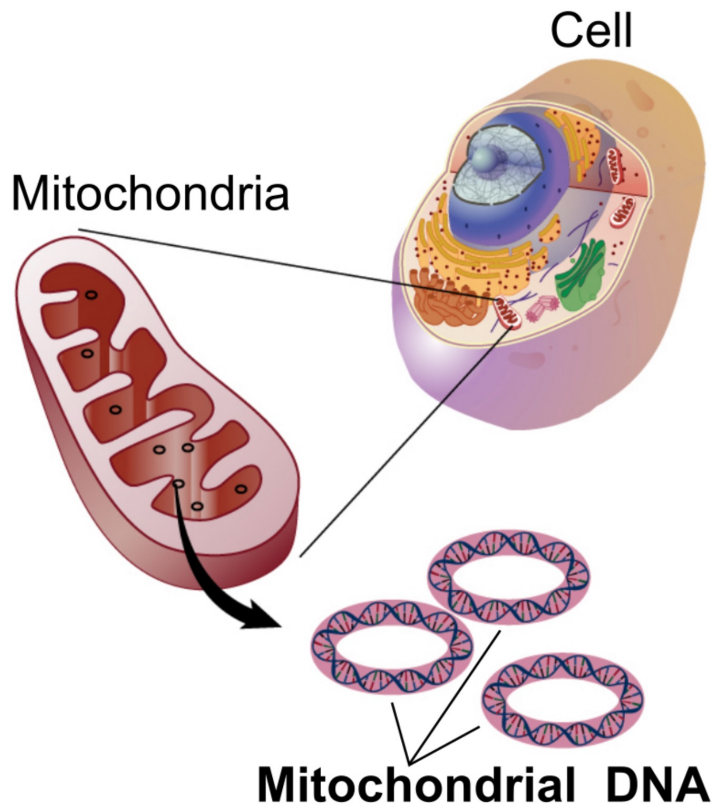
NIH National Institute of Environmental Health Sciences
Your Environment. Your Health.

Outline of Talk

- Function of mitochondrial DNA (mtDNA)
- How mtDNA is copied (POLG, POLG2, TWNK, SSBP1)
- How mutations arise in mitochondrial DNA, the natural evolution of mtDNA
- Genetic diseases (POLG related diseases) that affect mtDNA replication
- MtDNA mutagenesis in POLG related diseases
- New therapies on the horizon

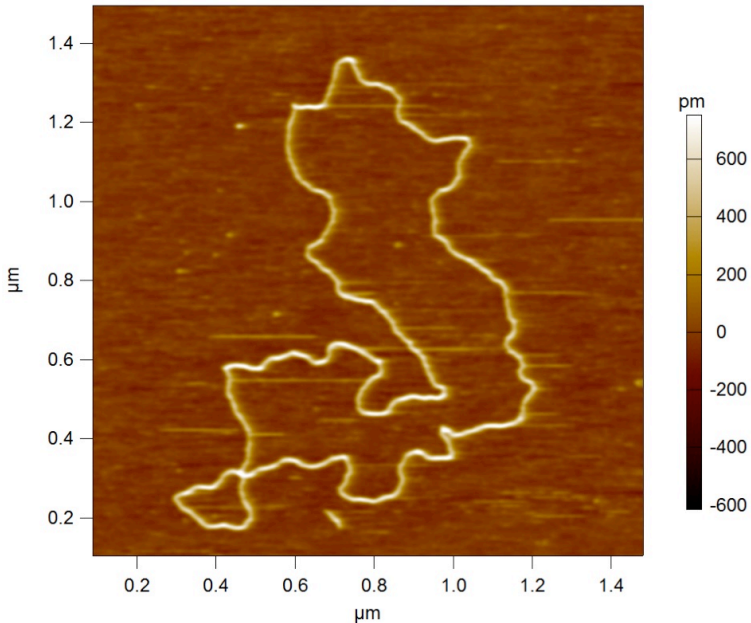
Mitochondria have their own DNA

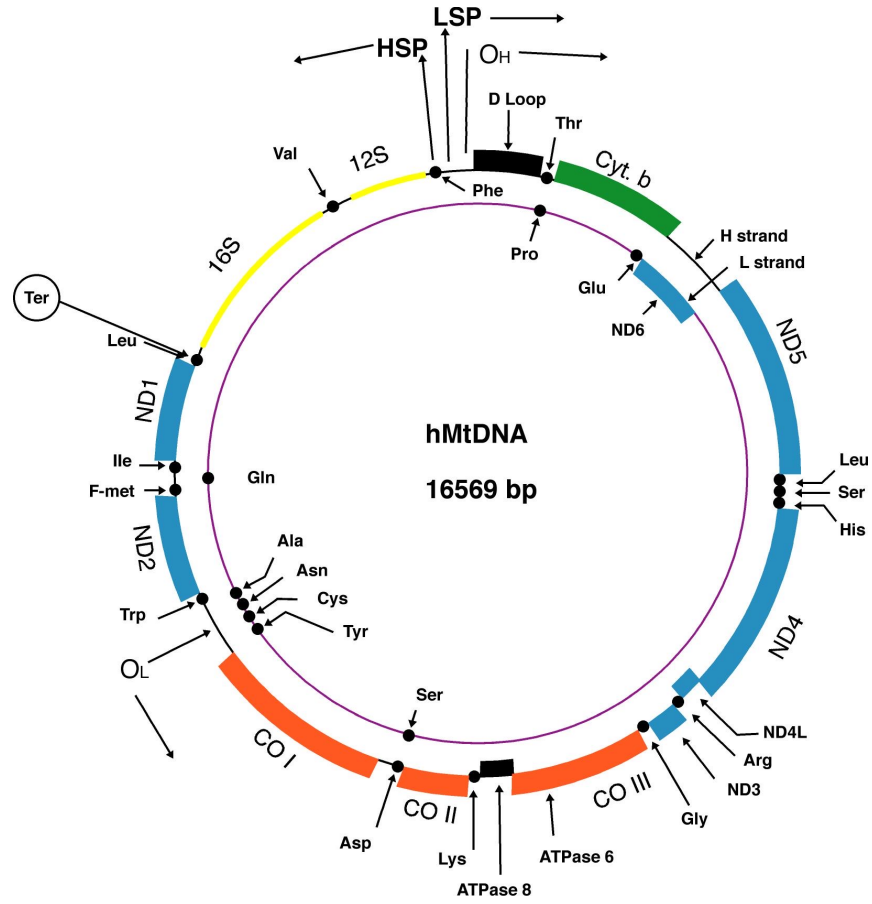


Human mitochondrial DNA

The mitochondrial genome is a closed, circular DNA.

Maternally inherited





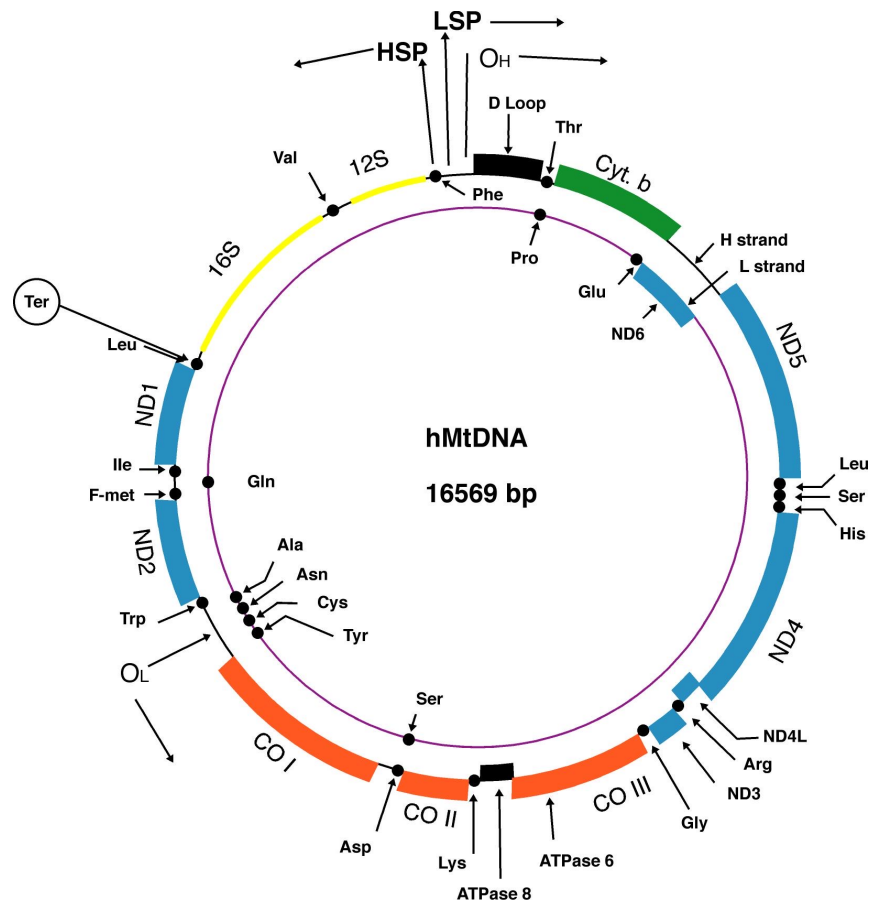
Human mitochondrial DNA

The mitochondrial genome is a closed, circular DNA.

Maternally inherited

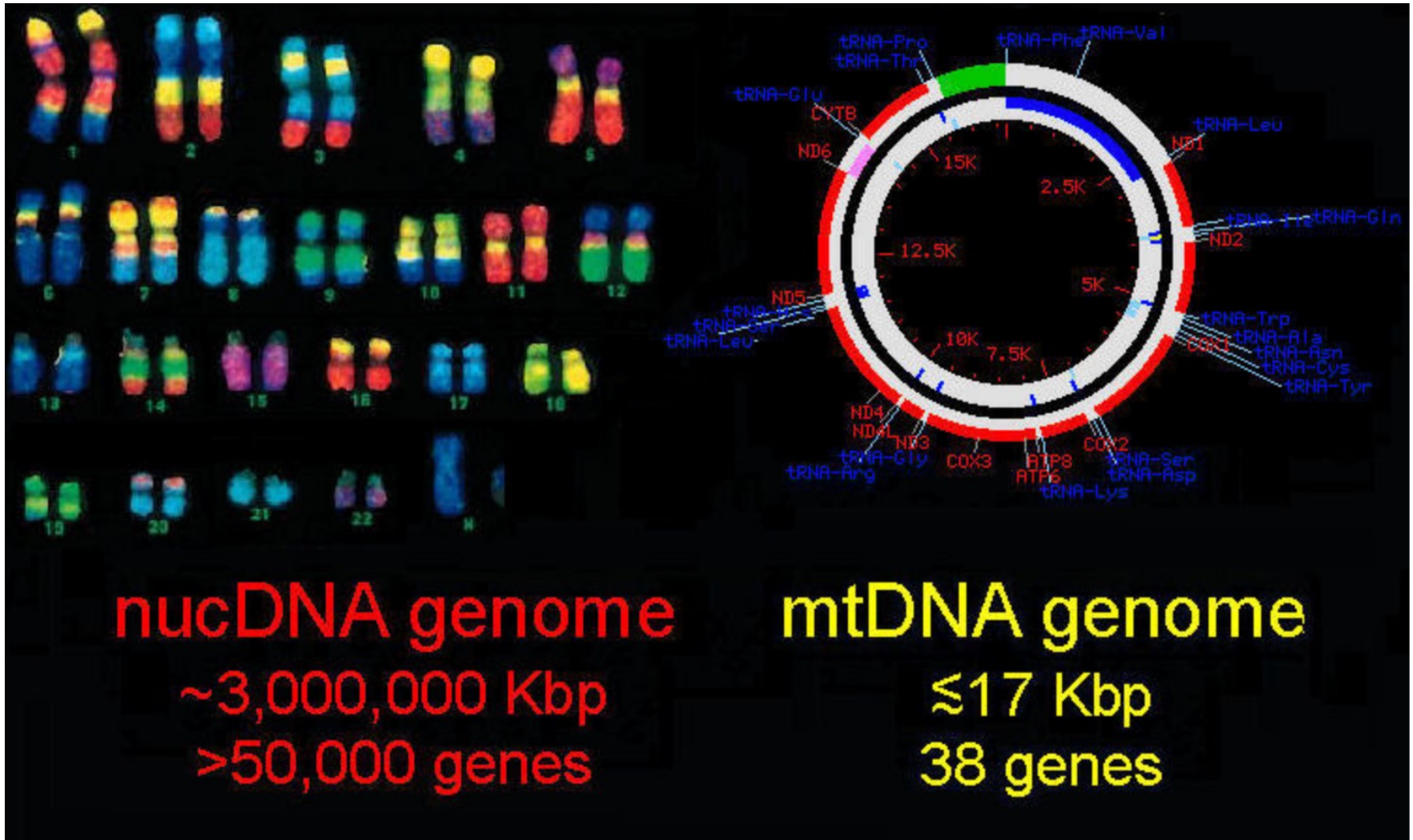
Thousands of copies per cell

MtDNA copy number is very dynamic

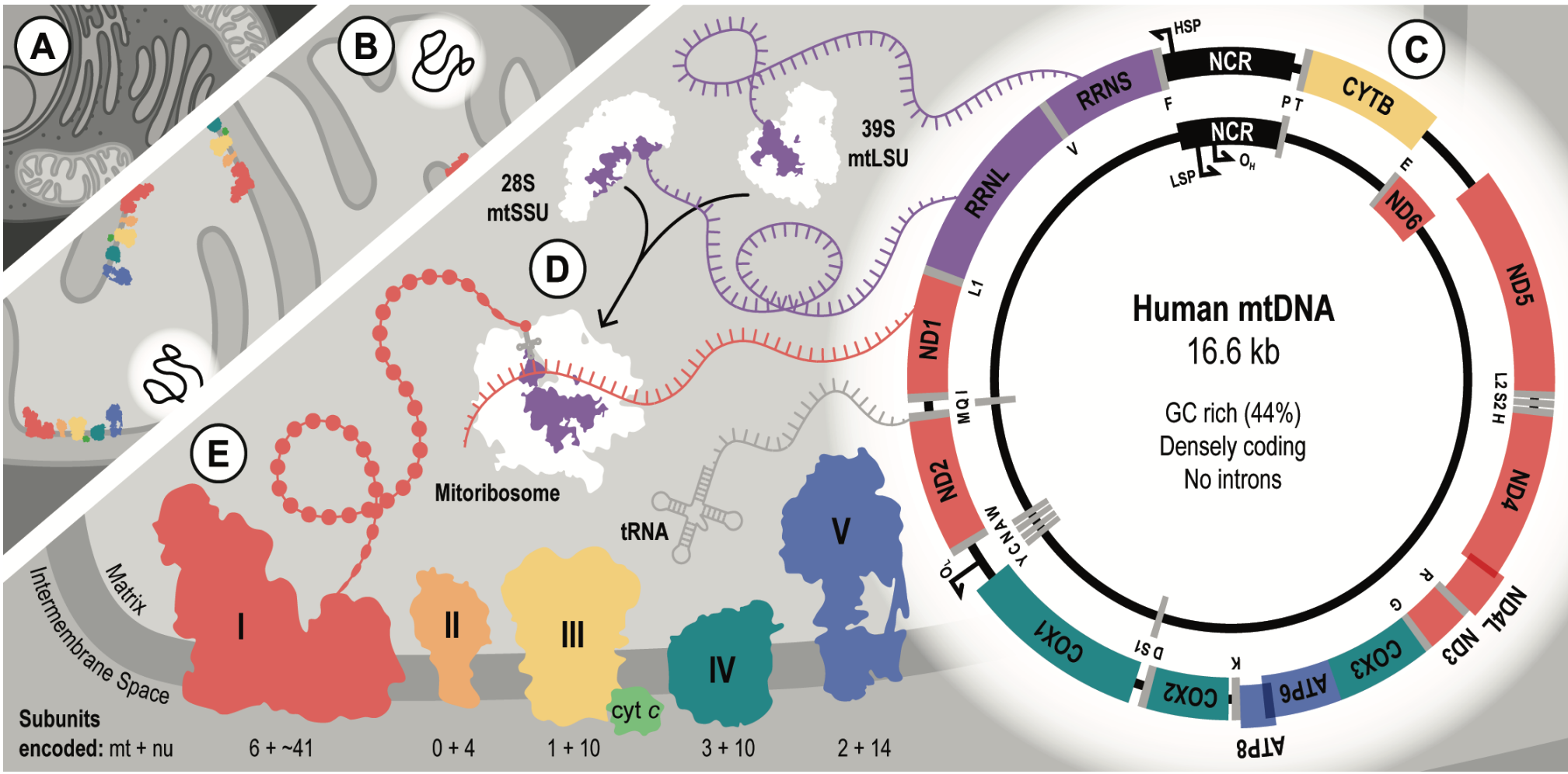


Nuclear vs. Mitochondrial DNA

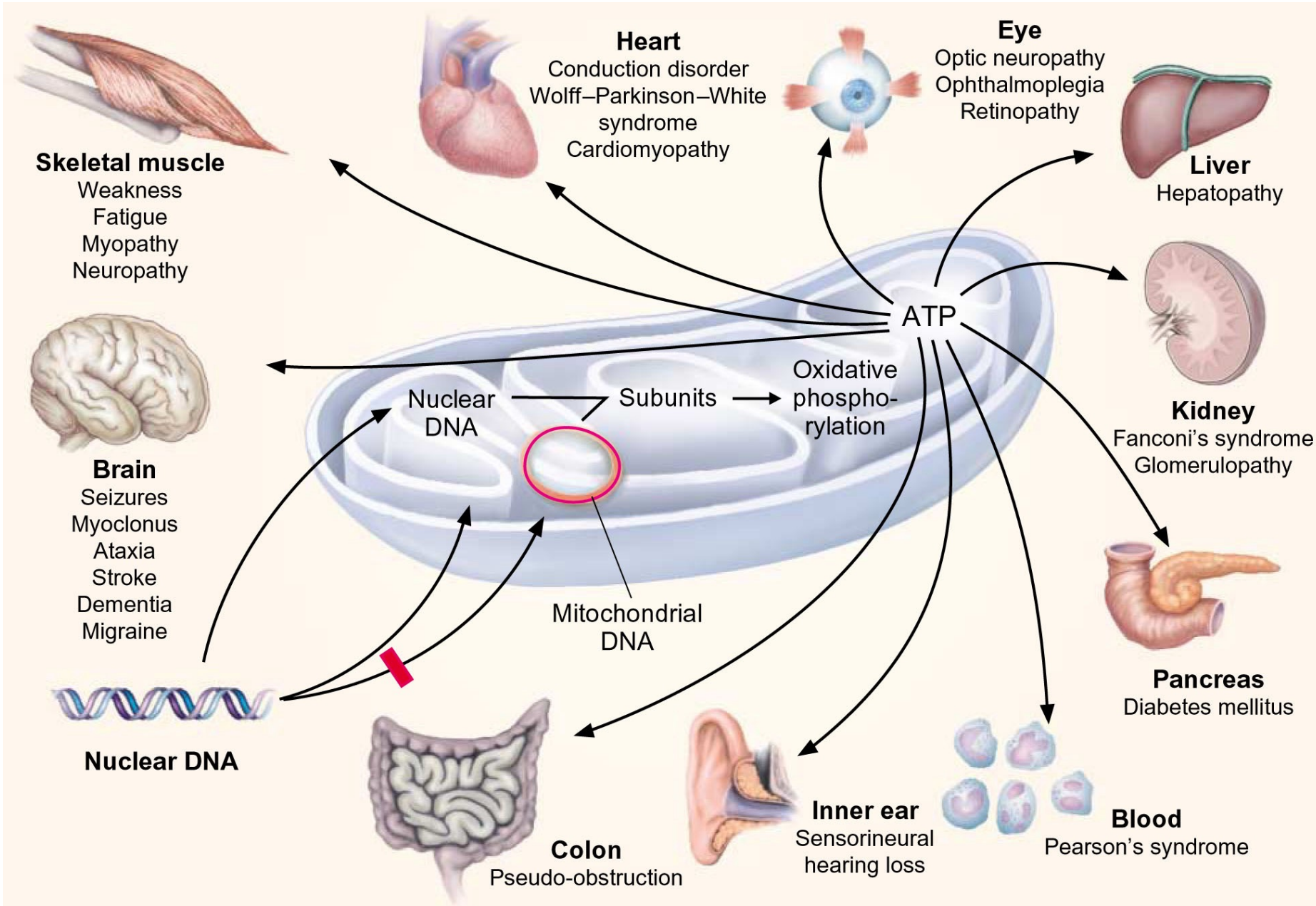
Mitochondrial DNA only accounts for ~0.3% of DNA in a cell



Human mitochondrial DNA



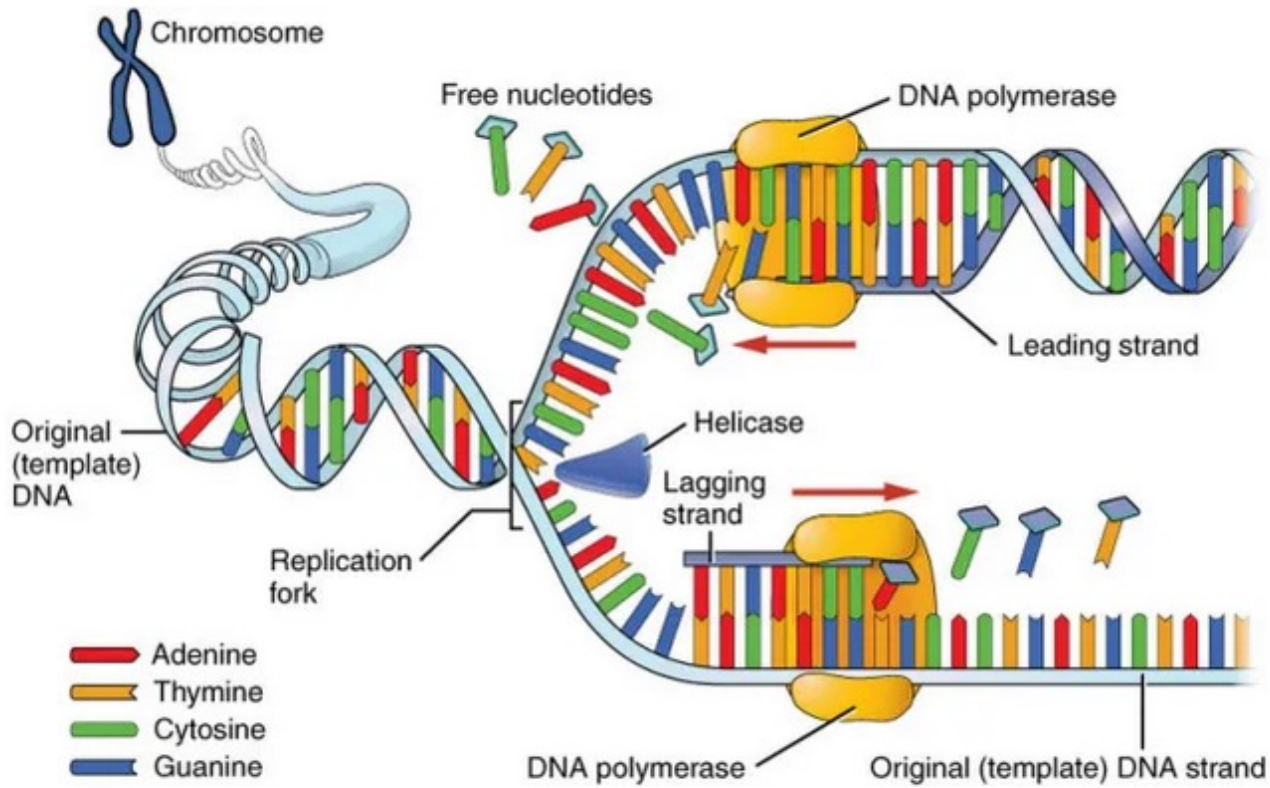
Gustafson et al., DNA Repair, 2020



from Johns DR 1995 NEJM 333:638-644

How is DNA copied

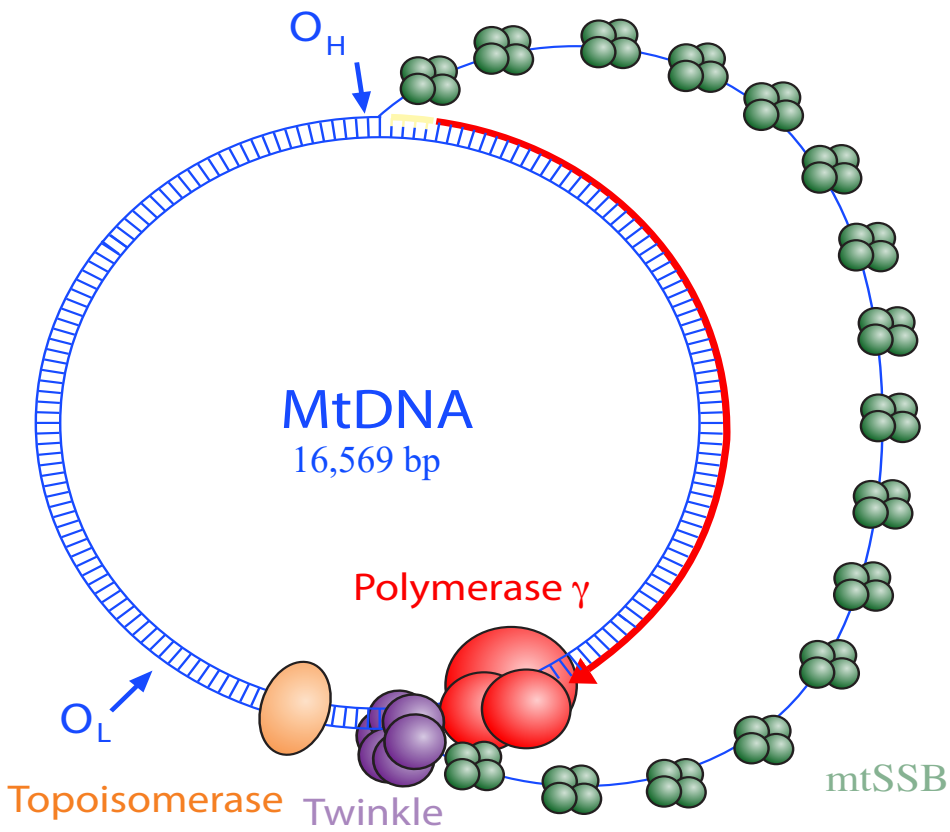
DNA is copied or replicated by enzymes called “DNA Polymerases”

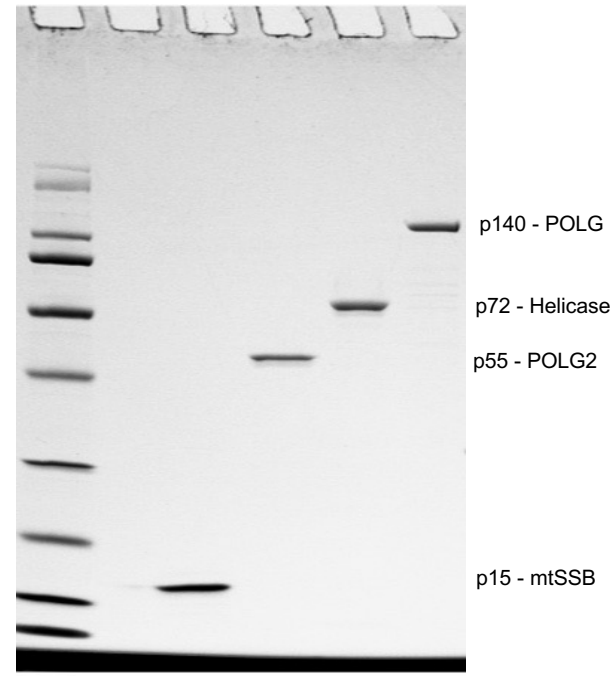


17 Human DNA Polymerases

Polymerase	Family	Chromosome	Mol. Wt. (kDa)	Function/Comments
α (alpha)	B	Xq21.3-q22.1	165	Initiates replication
β (beta)	X	8p12-p11	39	BER, other functions
γ (gamma)	A	15q25	140	Mitochondrial replication & repair
δ (delta)	B	19q13.3-.4	125	Replication, BER, NER, MMR
ε (epsilon)	B	12q24.3	255	Replication, checkpoint control
ζ (zeta)	B	6q22	344	yREV3 homolog, lesion bypass
η (eta)	Y	6p21.1	78	Lesion bypass, *XPV*, skin cancer susceptibility
θ (theta)	A	3q13.31	300	crosslink repair, *Dm308*, lesion bypass
ι (iota)	Y	18q21.1	80	Lesion bypass? BER?
κ (kappa)	Y	5q13.1	99	Lesion bypass, mutator when overexpressed
λ (lambda)	X	10q23	64	pol β homolog, meiosis? NHEJ
μ (mu)	X	7p13	55	TdT homolog, NHEJ
n (nu)	A	4p16.3	100	lesion bypass, crosslink repair?
σ (sigma)	X	5p15	60	TRF4
Rev1	Y	2q11.1-.2	125	lesion bypass
TdT	X	10q23-24	57	Terminal transferase
PrimPol	AEP	4q35.1	65	Restart during replication stress, Mitochondrial TLS

Proteins involved in mitochondrial DNA replication

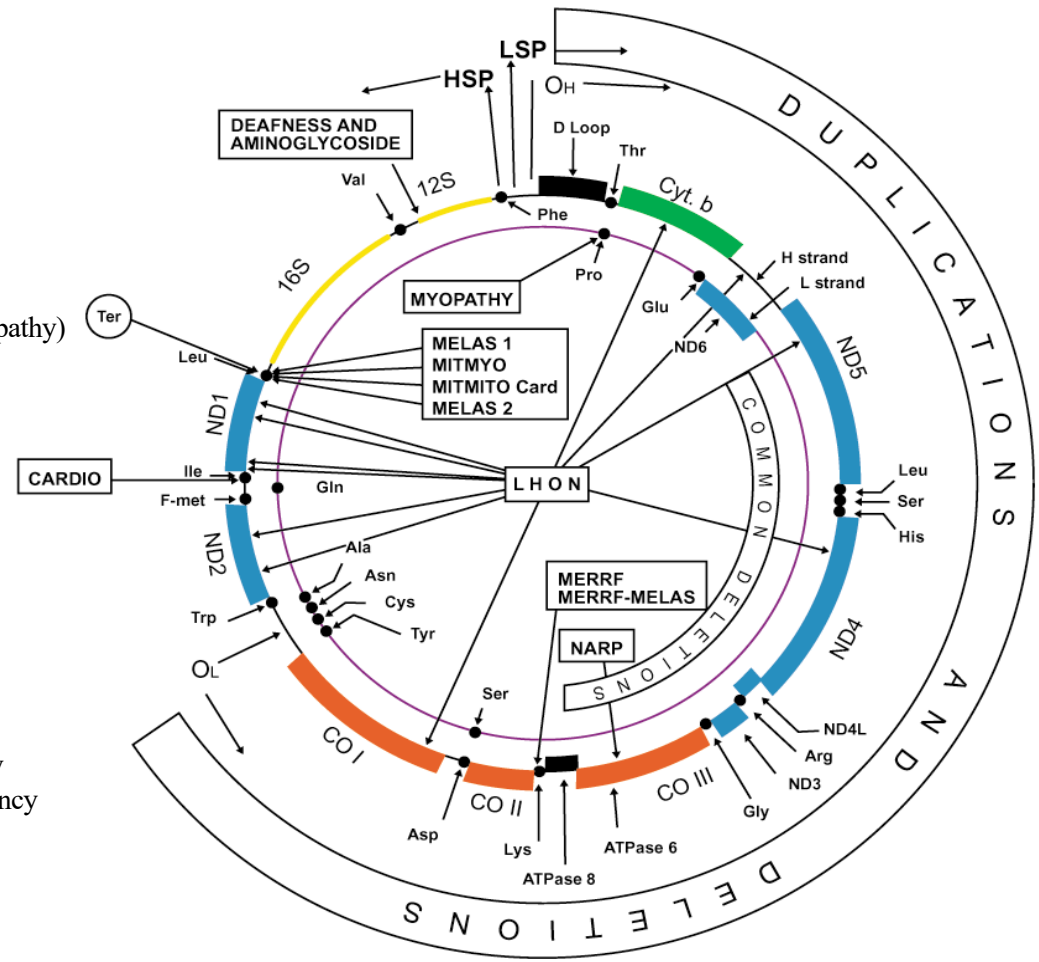


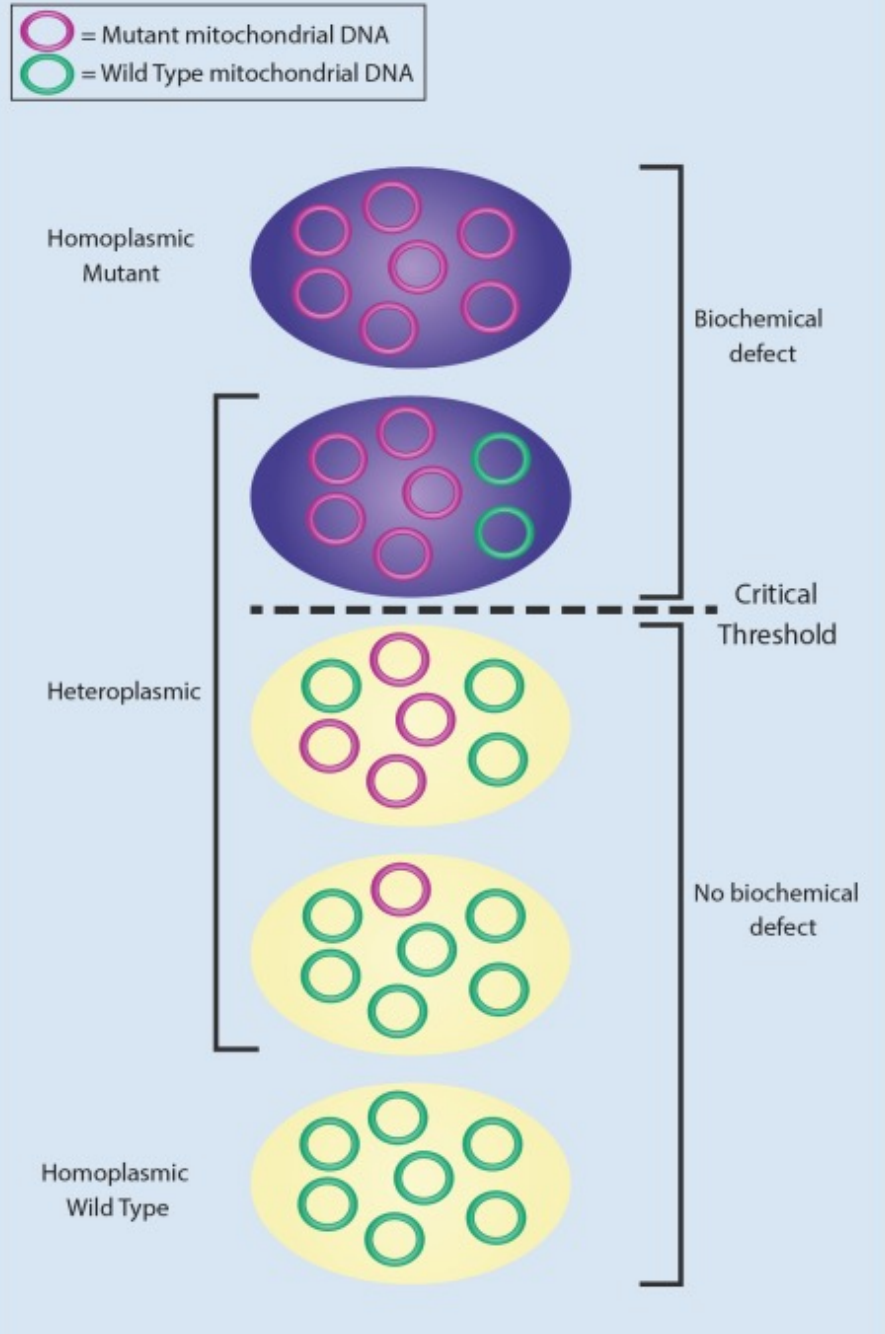


POLG: p140, catalytic subunit of Pol γ, polymerase and exonuclease
POLG2: p55, accessory subunit of Pol γ, functions as processivity factor
TWNK: replicative DNA helicase
SSBP1: single-stranded DNA binding protein

Mitochondrial DNA mutations cause or are associated with various diseases

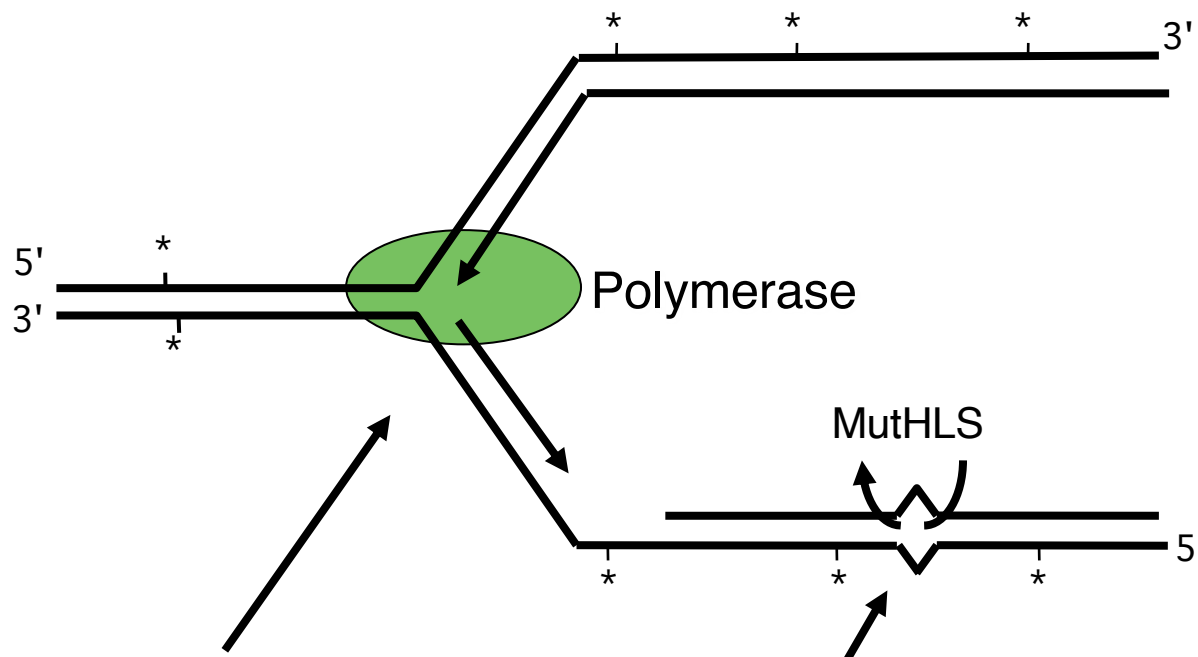
* Alpers Disease
* Barth syndrome
* Beta-oxidation Defects
* Carnitine-Acyl-Carnitine Deficiency
* Carnitine Deficiency
* Co-Enzyme Q10 Deficiency
* Complex I Deficiency
* Complex II Deficiency
* Complex III Deficiency
* Complex IV Deficiency
* Complex V Deficiency
* COX Deficiency
* CPEO
* CPT I Deficiency
* CPT II Deficiency
* Glutaric Aciduria Type II
* KSS
* Lactic Acidosis
* LCAD
* LCHAD
* Leigh Disease or Syndrome
* LHON
* LIC (Lethal Infantile Cardiomyopathy)
* Luft Disease
* MAD
* MCAD
* MELAS
* MERRF
* Mitochondrial Cytopathy
* Mitochondrial DNA Depletion
* Mitochondrial Encephalopathy
* Mitochondrial Myopathy
* MNGIE
* NARP
* Pearson Syndrome
* Pyruvate Carboxylase Deficiency
* Pyruvate Dehydrogenase Deficiency
* Respiratory Chain
* SCAD
* SCHAD
* VLCAD




= Mutant mitochondrial DNA
= Wild Type mitochondrial DNA
Homoplasmic Mutant
Biochemical defect
Critical Threshold
Heteroplasmic
No biochemical defect
Homoplasmic Wild Type

MtDNA mutates or evolves faster than nuclear DNA, with estimates suggesting that MtDNA mutates/evolves ~20-100-fold faster than nuclear DNA

Fidelity of nuclear DNA Replication: 10^{-10}



1. Insertion fidelity (DNA polymerase): 10^{-5}
2. Proofreading (*Exonuclease*): 10^{-2}
3. DNA mismatch repair: 10^{-3}

1. Typing
2. Delete (backspace)
3. Spell check

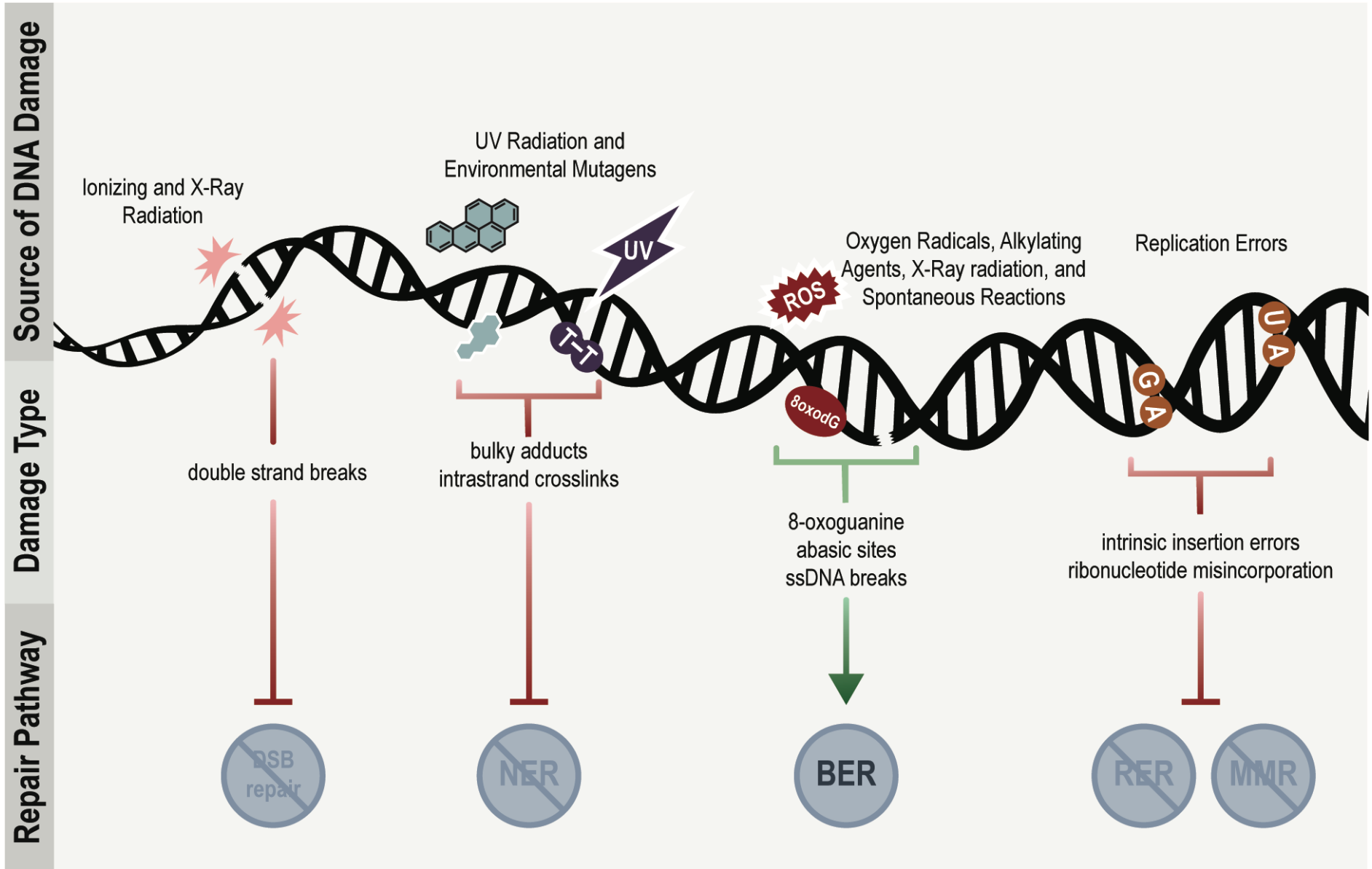
Fidelity of Human DNA Polymerase γ

- DNA polymerase γ has high DNA synthetic fidelity at single base pairs. (<1 error per 1,000,000 nucleotides synthesized)
- Pol γ proofreading contributes ~100-fold to base substitution and frameshift fidelity.

The fidelity of human DNA polymerase gamma with and without exonucleolytic proofreading and the p55 accessory subunit.
Longley MJ, Nguyen D, Kunkel TA, Copeland WC. J Biol Chem. 2001 Oct 19;276(42):38555-62

Nuclear and Mitochondrial DNA Repair

Repair system	Nuclear	Mitochondrial
Nucleotide Excision Repair	XPA, XPC, RPA, TFIIH, XPF9, XPG Pol ε, PCNA, RFC, DNA ligaseI/III	None
Mis Match Repair	hMSH2, hMSH3, hMSH5, hMSH6, hMLH1, PMS2	No clear MMR activity
Base Excision Repair	Base glycosylase, UDG, TDG APE, PARP Short patch repair - polβ Long patch repair - polδ/ε or polβ FEN1, DNA2, PCNA, RFC DNA ligase I/III	UDG, OGG, hMYH APE1 Short patch repair – pol γ Long patch repair – pol γ, FEN1, DNA2, DNA ligase III
Ribonucleotide Excision Repair	Rnase H2	None

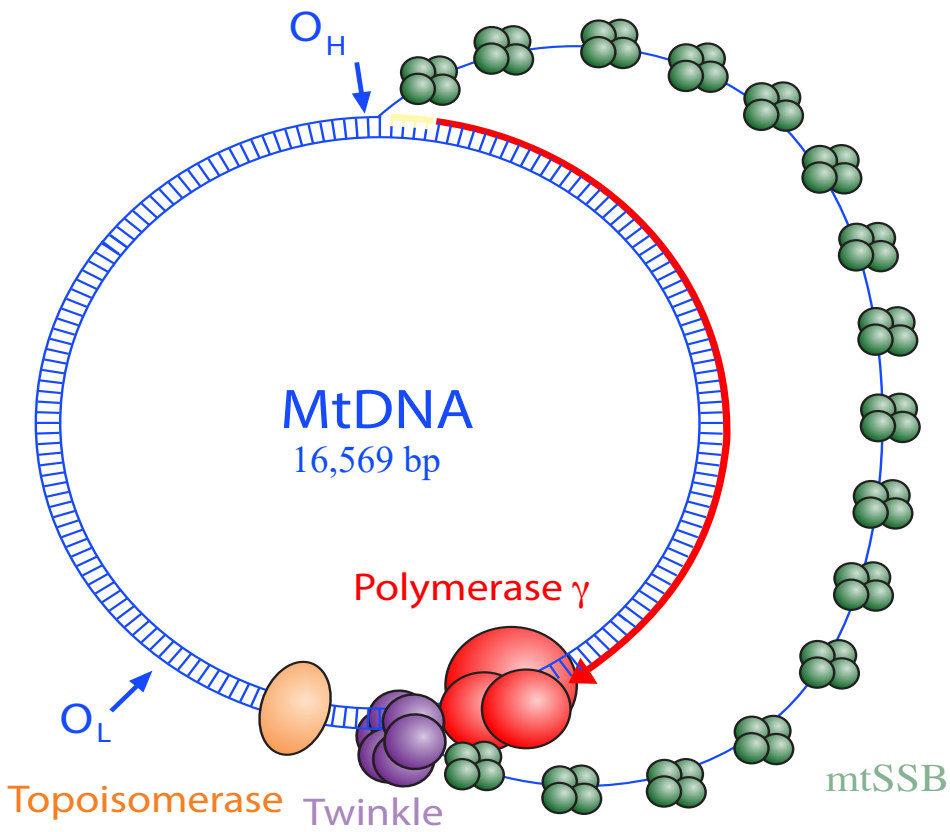

Source of DNA Damage
Damage Type
Repair Pathway
Ionizing and X-Ray Radiation
UV Radiation and Environmental Mutagens
UV
T–T
ROS
Oxygen Radicals, Alkylating Agents, X-Ray radiation, and Spontaneous Reactions
Replication Errors
8oxodG
G
A
U
A
double strand breaks
bulky adducts intrastrand crosslinks
8-oxoguanine abasic sites ssDNA breaks
intrinsic insertion errors ribonucleotide misincorporation
DSB repair
NER
BER
RER
MMR

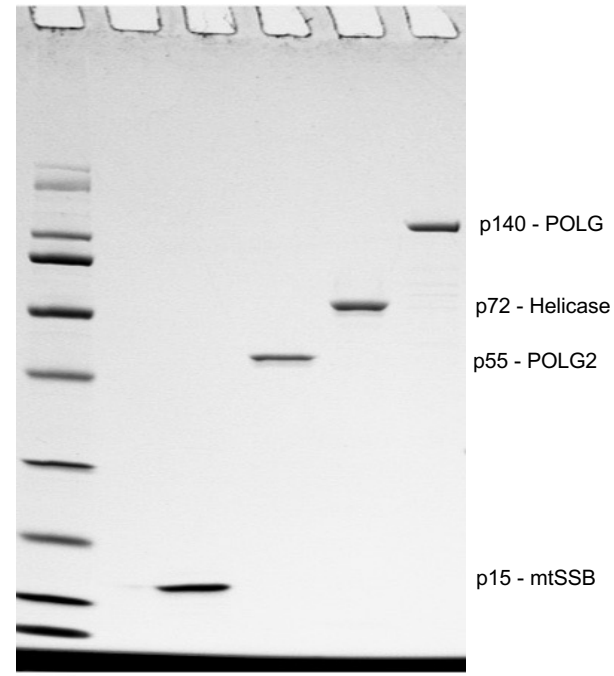
MtDNA mutates or evolves faster than nuclear DNA, with estimates suggesting that MtDNA mutates/evolves ~20-100-fold faster than nuclear DNA

The highly mutation rate is mostly due to the lack of mitochondrial mismatch repair.

The major driver of mtDNA mutations is spontaneous errors of mtDNA replication from POLG

Proteins involved in mitochondrial DNA replication





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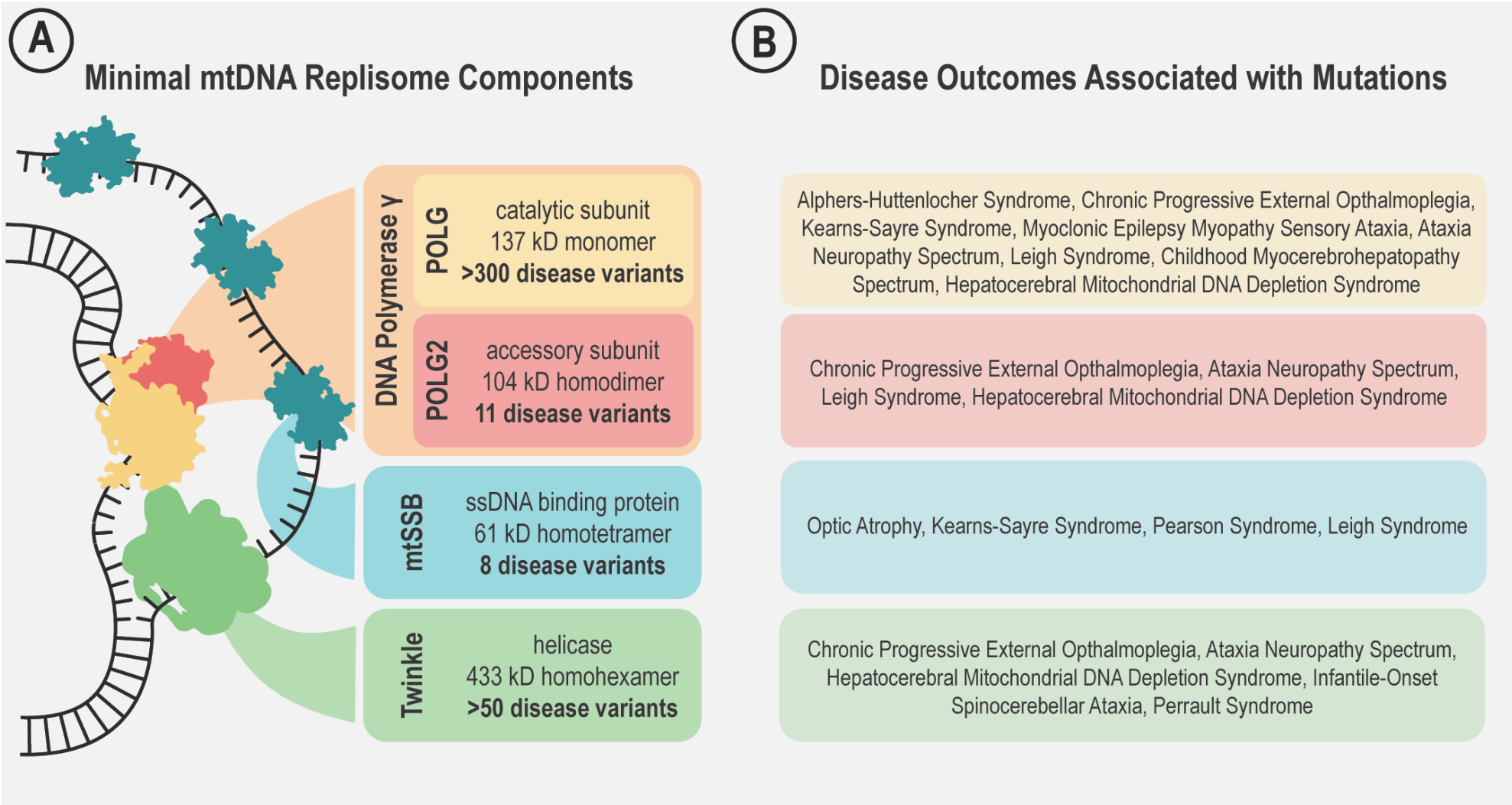
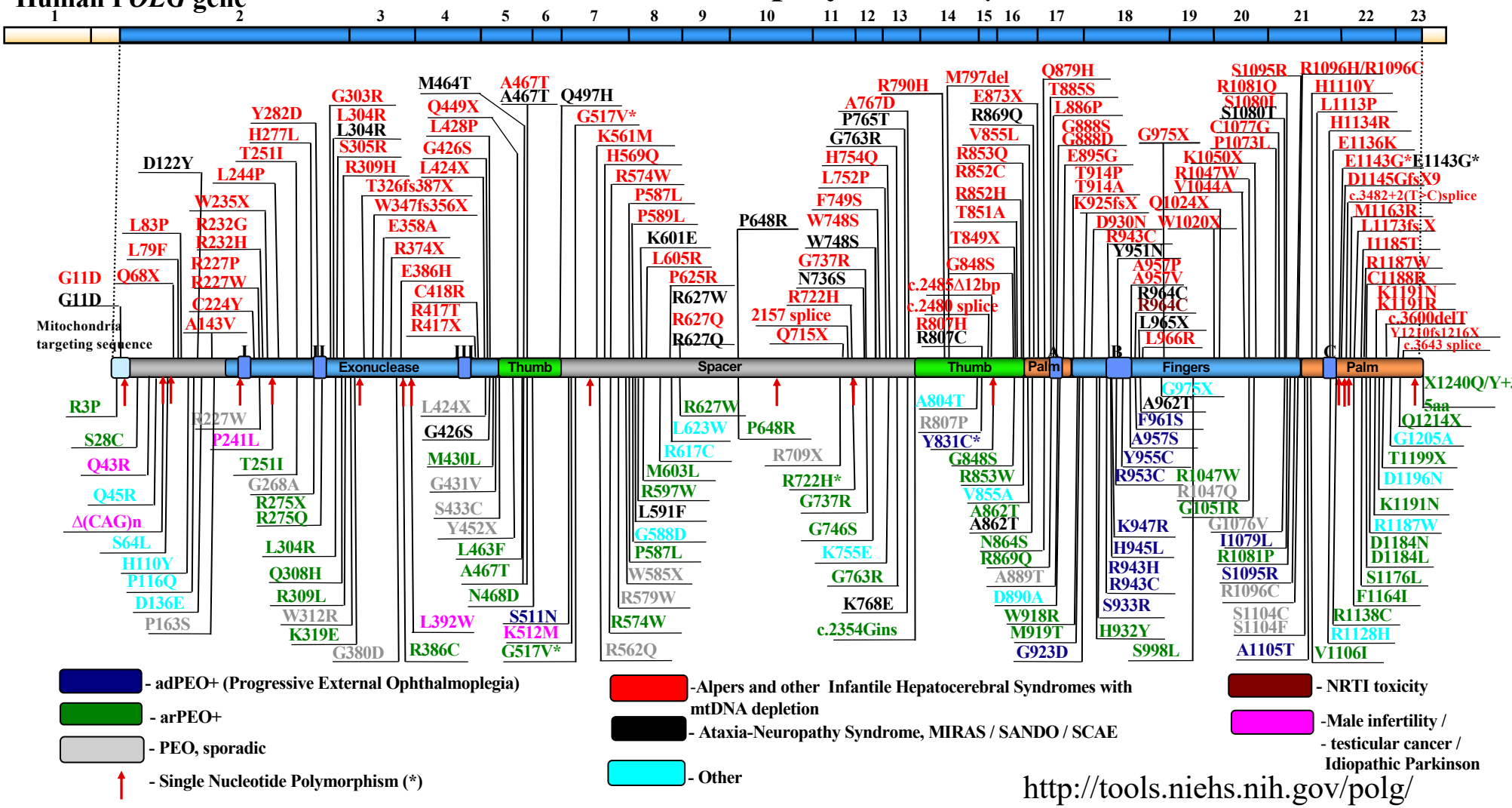

A
Minimal mtDNA Replisome Components
DNA Polymerase γ
POLG
catalytic subunit
137 kD monomer
>300 disease variants
POLG2
accessory subunit
104 kD homodimer
11 disease variants
mtSSB
ssDNA binding protein
61 kD homotetramer
8 disease variants
Twinkle
helicase
433 kD homohexamer
>50 disease variants
B
Disease Outcomes Associated with Mutations
Alphers-Huttenlocher Syndrome, Chronic Progressive External Opthalmoplegia, Kearns-Sayre Syndrome, Myoclonic Epilepsy Myopathy Sensory Ataxia, Ataxia Neuropathy Spectrum, Leigh Syndrome, Childhood Myocerebrohepatopathy Spectrum, Hepatocerebral Mitochondrial DNA Depletion Syndrome
Chronic Progressive External Opthalmoplegia, Ataxia Neuropathy Spectrum, Leigh Syndrome, Hepatocerebral Mitochondrial DNA Depletion Syndrome
Optic Atrophy, Kearns-Sayre Syndrome, Pearson Syndrome, Leigh Syndrome
Chronic Progressive External Opthalmoplegia, Ataxia Neuropathy Spectrum, Hepatocerebral Mitochondrial DNA Depletion Syndrome, Infantile-Onset Spinocerebellar Ataxia, Perrault Syndrome

Nuclear loci that affect the stability of mitochondrial DNA

Gene	Disorder	Locus	Function
mtDNA replication and repair			
POLG	PEO, Alpers, ataxia	15q25	Pol γ catalytic subunit
POLG2	PEO	17q23-24	Pol γ accessory subunit
TWNK	PEO, mtDNA depletion, IOSCA	10q24	Mitochondrial DNA helicase
MGME1	PEO, mtDNA depletion	20p11.23	Single-strand DNA nuclease
DNA2	mtDNA deletions, PEO	10q21.3-22.1	Mito/nuclear helicase-nuclease
RNASEH1	encephalomyopathy, mtDNA deletions	2p25	RNA/DNA hybrid endoribonuclease
TFAM	mtDNA depletion	10q21.1	Organizes mtDNA transactions
SSBP1	Optic autrophy, mtDNA dep/del	7q34	Single strand DNA binding protein
nucleotide pool metabolism			
ANT1	PEO	4q34-35	Adenine nucleotide translocator
TP	MNGIE, mtDNA deletions/depletion	22q13.32	Thymidine phosphorylase
DGUOK	mtDNA depletion	2p13	Deoxyguanosine kinase
TK2	PEO, mtDNA depletion	16q22-23.1	Mitochondrial thymidine kinase
MPV17	mtDNA deletions, depletion	2p23.3	Mito inner membrane protein
SUCLA2	mtDNA depletion	13q14.2	ATP-dep Succinate-CoA ligase
SUCLG1	mtDNA depletion	2p11.2	GTP-dep Succinate-CoA ligase
RRM2B	PEO, mtDNA depletion	8q23.1	p53-Ribonucleotide reductase, small subunit
ABAT	mtDNA deletions, depletion	16p13.2	4-Aminobutyrate aminotransferase
mitochondrial homeostasis / dynamics			
OPA1	Dominant optic atrophy, mtDNA deletions, ataxia	3q28-29	Dynamin related GTPase
MFN2	DOA, mtDNA deletions	1p36.22	Mitofusin 2
FBXL4	mtDNA depletion, encephalopathy	6q16.1-16.3	Mitochondrial LLR F-Box protein
AFG3L2	Spinocerebellar ataxia, mtDNA deletions	18p11.21	Mitochondrial IM metalloprotease
SPG7	ataxia, spastic paraplegia	16:89.49-89.56	Mito IM metalloprotease component
GFER	mtDNA deletions, myopathy	16:1.98-1.99	Protein import to IMS

Mutations in DNA polymerase γ, *POLG*



POLG Disease Burden

- *POLG* mutations are the most common cause of inherited mitochondrial disorders (Saneto and Naviaux, 2010).
- Approximately 2% of the population carries a pathogenic genetic variant of *POLG* (Saneto and Naviaux, 2010).
- The combined prevalence of recessive and dominant disease caused by *POLG* mutations is ~1:10,000.

Major clinical syndromes associated with *POLG* mutations

Age of Onset	Syndrome	mtDNA defect
Neonatal/Infancy	Myocerebrohepatopathy spectrum (MCHS)	Depletion
Infancy/Childhood	Alpers-Huttenlocher syndrome (AHS)	Depletion
Adolescent/young adult	Ataxia neuropathy spectrum (ANS)	Deletions
	Myoclonus, epilepsy, myopathy, sensory ataxia (MEMSA)	Deletions
	Progressive external ophthalmoplegia (PEO) with or without sensory ataxic neuropathy and dysarthria (SANDO)	Deletions

T251I + P587L in the Literature

Allele 1	Allele 2	Sex	Age of Onset (yr)	Clinical Phenotype	Reference
T251I+P587L	T251I+P587L	F	41	PEO	Stewart JD, et al. (2009)
T251I+P587L	T251I+P587L	M	63	PEO & myopathy	Horvath R, et al. (2006).
T251I+P587L	G848S	M	0.5	Alpers	Wong LJ, et al. (2008)
T251I+P587L	G848S	F	51	PEO	Blok MJ, et al. (2009)
T251I+P587L	G848S	M	73	SANDO	Weiss MD, et al.(2010)
T251I+P587L	L304R	F	45	PEO, ataxia & myopathy	Horvath et al. (2006)
T251I+P587L	L304R	M	60	PEO & neuropathy	Horvath, et al. (2006)

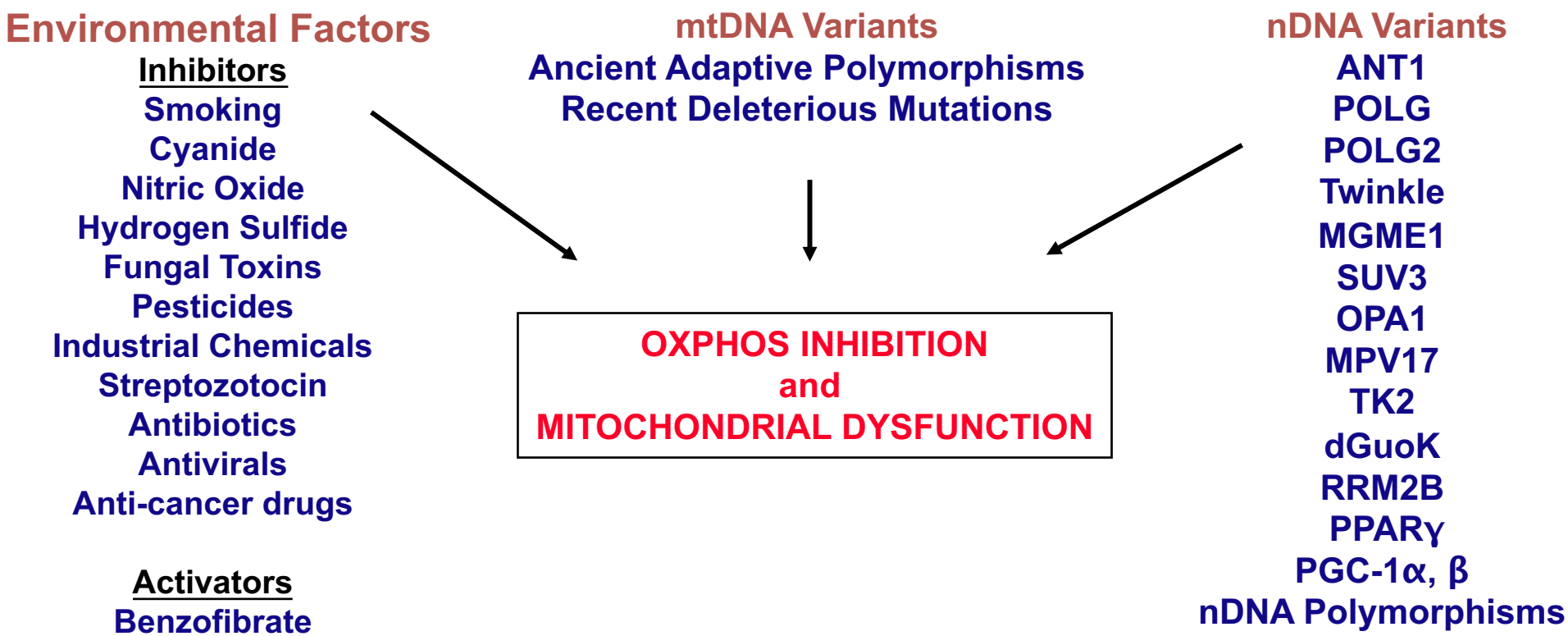
Table 1. Summaries of the case histories of the four patients. Homozygous A467T patients

	Patient 1	Patient 2	Patient 3	Patient 4
Age at presentation (years)	3	6	20	24
Age at death (years)	5.5	Alive at 16	44	Alive at 31
Symptoms at presentation	Seizures	Encephalitis-type presentation	Diplopia	Seizures
Clinical phenotype	Alpers-Huttenlocher	MEMSA+	SANDO	"MELAS-like"
Blood/CSF results	GGT 170 IU/l (reference <20 IU/L), AST 490 IU/L (reference range 5 to 45 IU/l)	↑lactate 2.6mmol/L (<2) Liver function normal; ↑Plasma alanine 537 mcmol/L (150–450); ↓Plasma arginine 28 mcmol/L (40–120); CSF lactate 1.6mmol/L (<2); ↑CSF protein 1.32 g/L (0.15–0.6); CSF 5MTHF 29 (46–120)	↑ lactate 2.3mmol/L (< 1.65); CK 329	Normal lactate; Normal CSF exam
Neurophysiology	-	EEG: Intermittent runs of rhythmic delta activity; CS: sensory neuropathy affecting legs	NCS: Severe axonal neuropathy	NCS: Moderately severe axonal sensory motor neuropathy
Radiology	Chronic grey matter ischaemia	MRI: Bilateral occipital lesions around calcarine sulci	-	MRI: Right occipital infarct
Neuropathology	Cortical degeneration in the occipital and parietal lobes, typical of PNDC. Bilateral hippocampal sclerosis. Hepatic microsteatosis	Brain biopsy: Non-specific; Muscle histology: COX-negative fibres	Muscle histology: ↑ no. of ragged red fibres and > 10 COX-negative fibres	Muscle histology: Ragged red fibres and COX-negative fibres and marked variation in fibre size with scattered groups of atrophic fibres.
Muscle Respiratory Chain enzymes	-	Complex I 0.126 (0.104–0.268); Complex II 0.159 (0.040–0.204); Complex IV 0.026 (0.014–0.034)	Complex I 0.170 (0.104–0.268); Complex II 0.077 (0.040–0.204); Complex IV 0.024 (0.014–0.034)	-

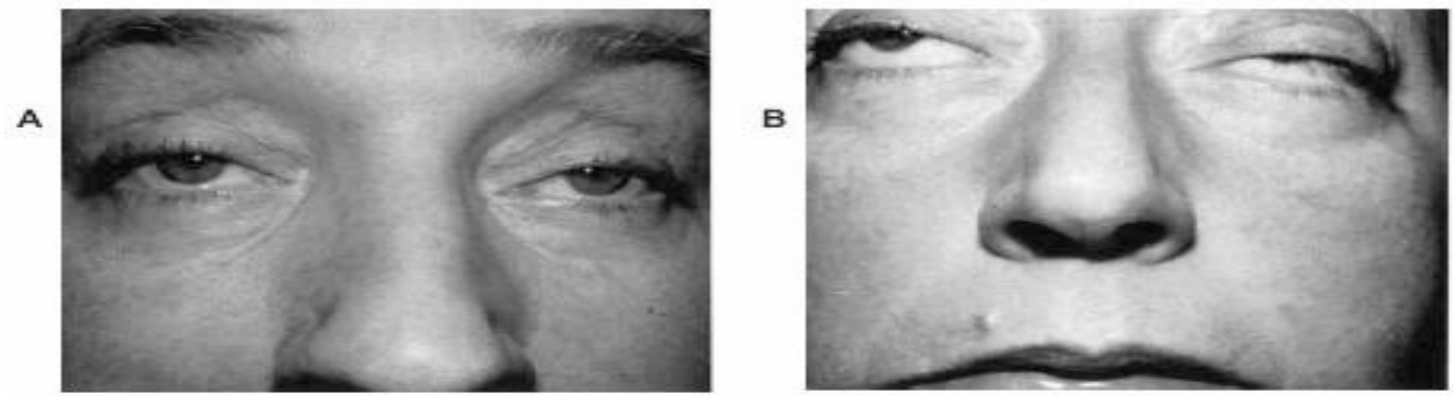
Key: 5MTHF, 5-methyltetrahydrofolate; AST, aspartate aminotransferase; COX, cytochrome oxidase; EEG, electroencephalogram; GGT, gamma-glutamyltranspeptidase; MELAS, mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes; MEMSA, myoclonic epilepsy, myopathy, sensory ataxia; NCS, nerve conduction studies; PNDC, progressive neuronal degeneration of childhood; SANDO, Sensory Ataxia Neuropathy Dysarthria Ophthalmoplegia.

Rajakulendran et al., 2016 Plos ONE

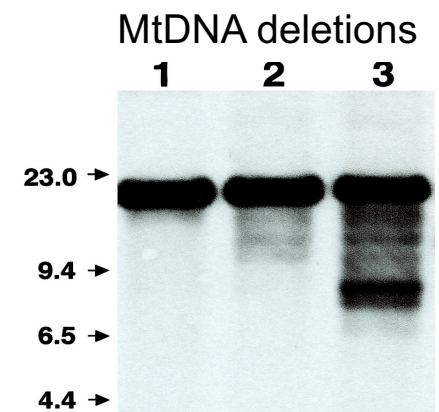
GENETIC & ENVIRONMENTAL INTERACTIONS RESULTING IN MITOCHONDRIAL DYSFUNCTION



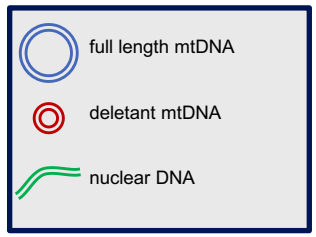
Progressive External Ophthalmoplegia

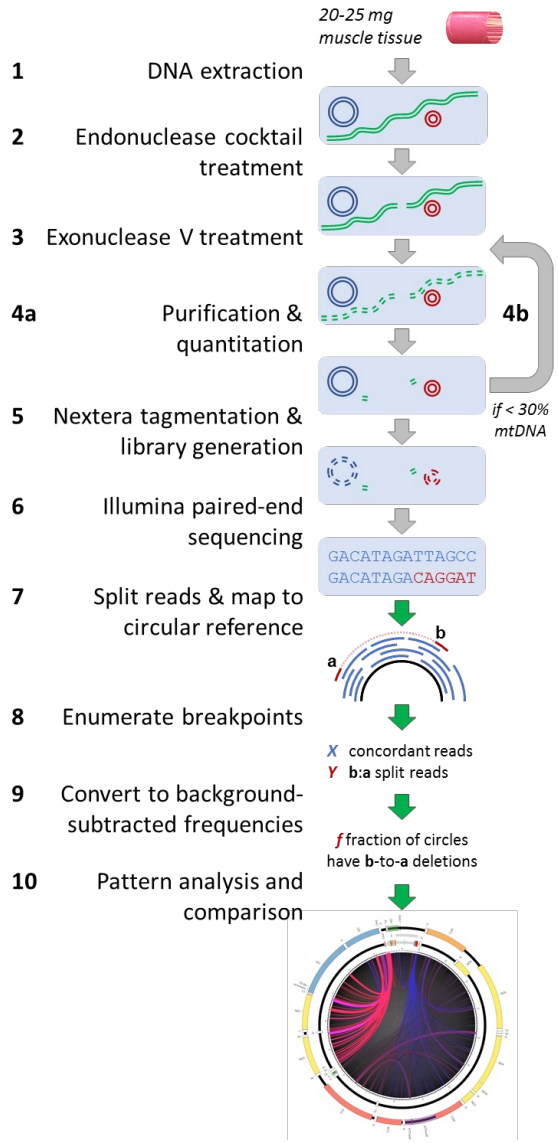


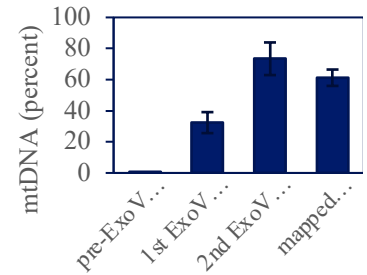
- Weakening of the external eye muscles
- Ophthalmoparesis, inability to look right and left
- Bilateral ptosis, droopy eyelids
- Multiple deletions in the mtDNA
- Many other associated symptoms



Pipeline for MtDNA Deletion Detection and Mapping: LostArc







LostArc TEAM

Scott Lujan
Matt Longley
Maggie Humble
Andy Lavender
Adam Burkholder
Robert Taylor, Newcastle, UK
Robert McFarland, Newcastle, UK
Grainne Gorman, Newcastle, UK
Doug Turnbull, Newcastle, UK
Tom Kunkel

Lujan et al., 2020 *Genome Biology* 21:248

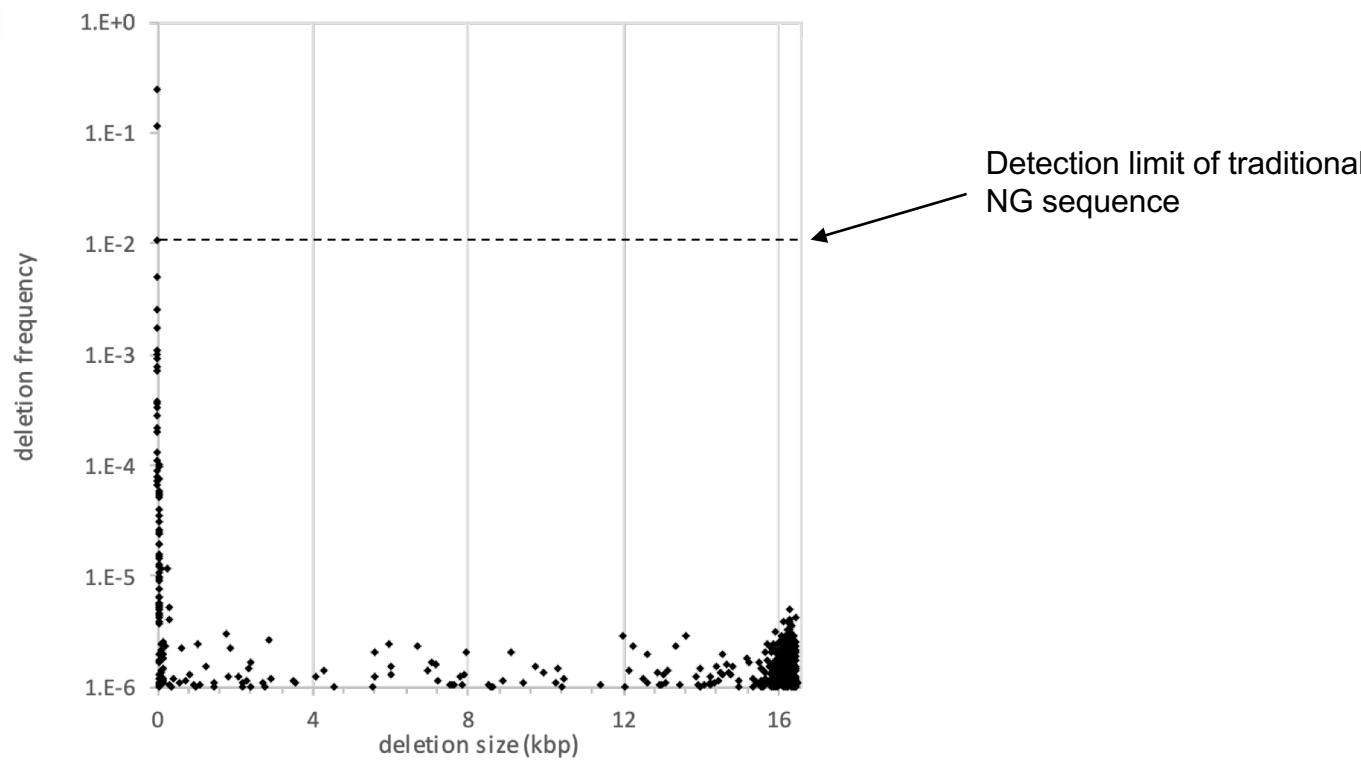
Analyzed

- 22 PEO patients with POLG mutations ranging in age from 17 – 80
- 19 Wildtype subjects, ages 19-93

Identified:

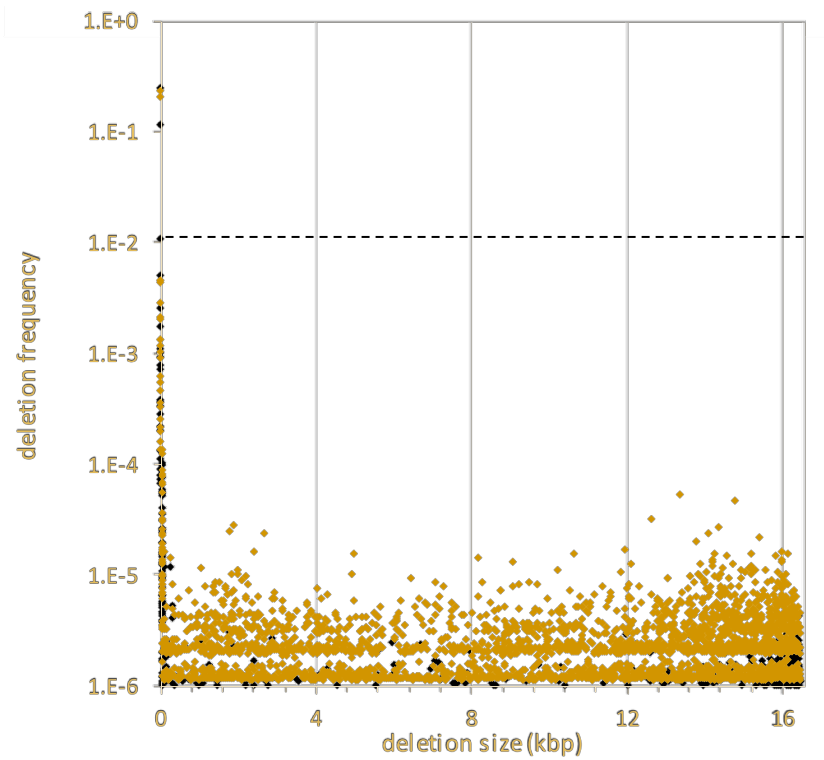
- 35 million mtDNA deletions
- 470,000 unique deletions

HEK293 cells (weighted mean, n = 3)



HEK293 cells (weighted mean, n = 3)

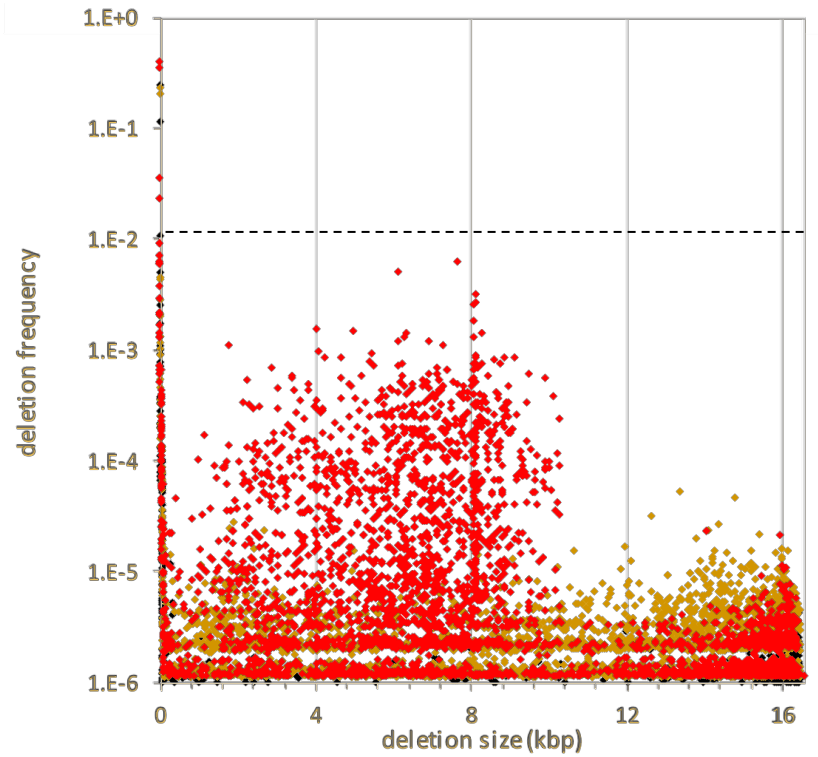
M314 (WT *POLG*, 17 years old at biopsy)



HEK293 cells (weighted mean, n = 3)

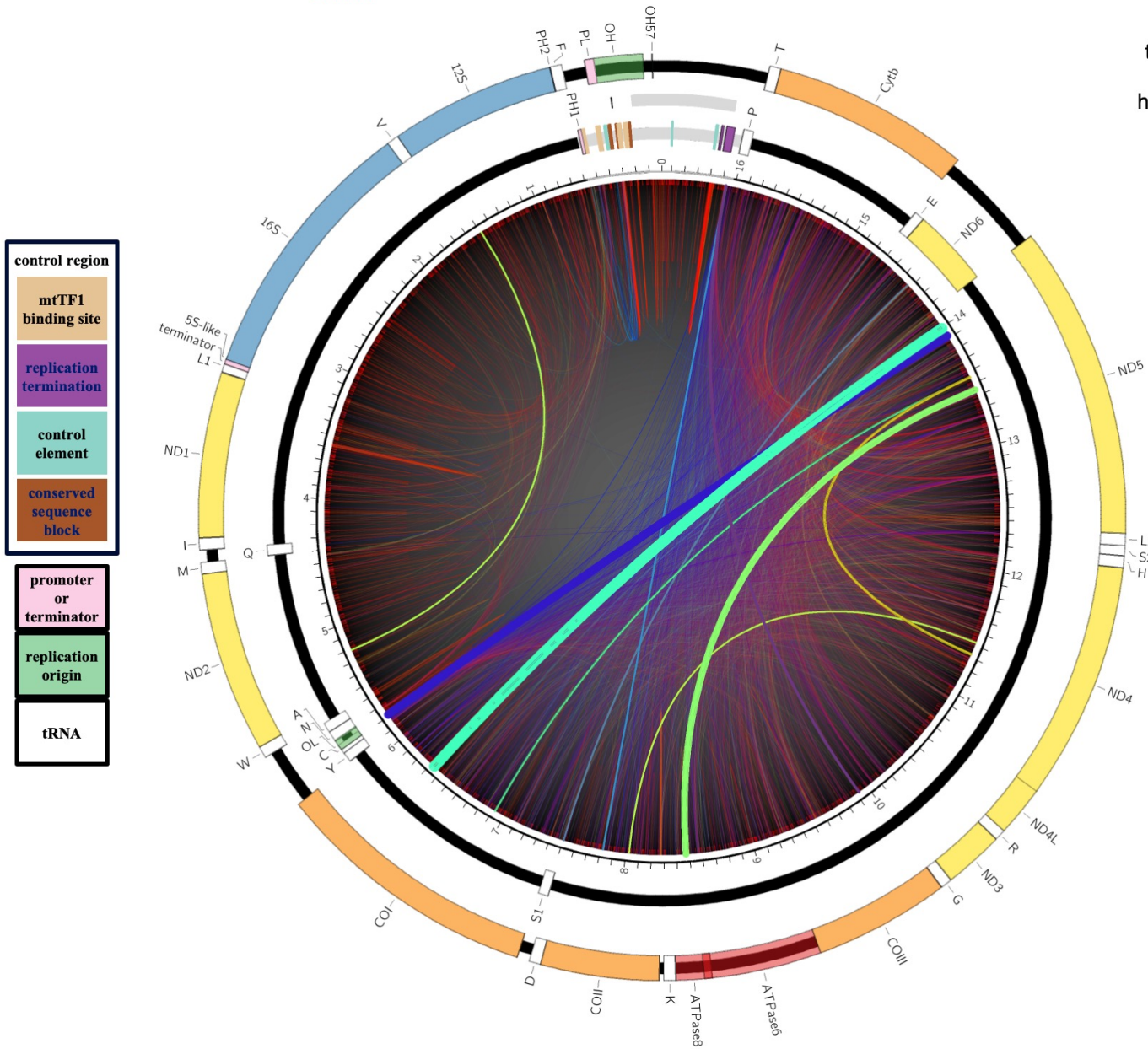
M314 (WT *POLG*, 17 years old at biopsy)

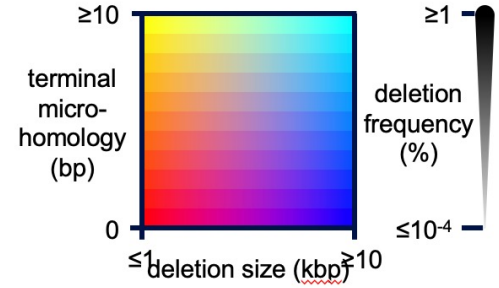
M508 (A467T/A467T *POLG*, 45 years old at biopsy)



>70% of the mtDNA genomes carried a deletion

45 y.o. PEO patient; A467T / T251I-P587L





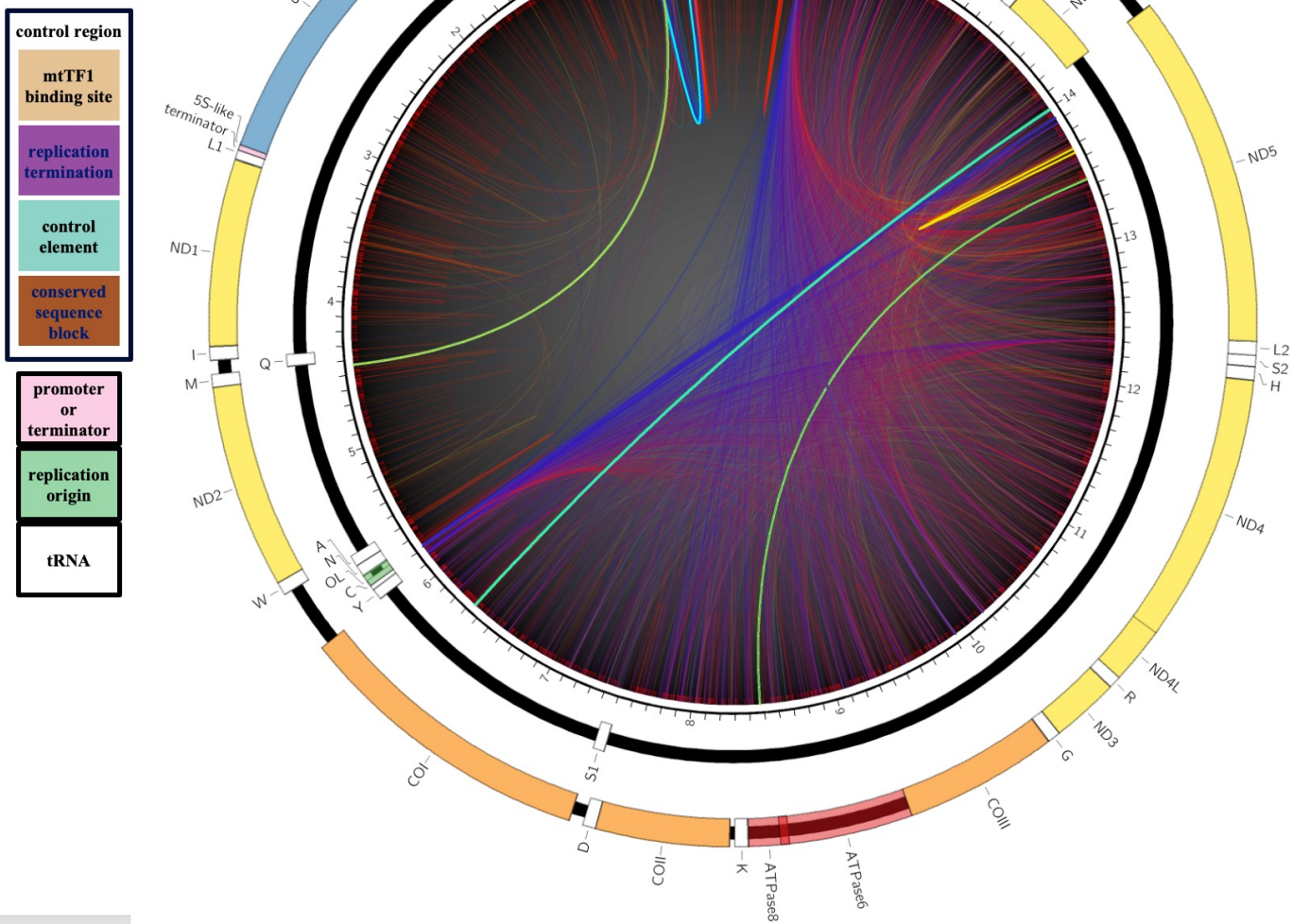
POLG A467T and T251I/P587L:

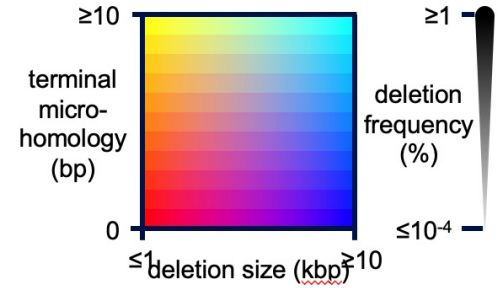
- Age of on-set at 45 yrs.
- Patient diagnosed with PEO, ptosis, and proximal weakness
- 25% COX negative muscle fibers and positive for ragged red fibers
- Long range PCR detected mtDNA deletions

Mito Deletion Mapping Results

- Over 87 million reads aligned
- 79% of the mtDNA genomes contained a deletion
- 446,000 deletions detected
- 25,933 unique deletions

49 y.o. PEO patient: W748S / R1096C





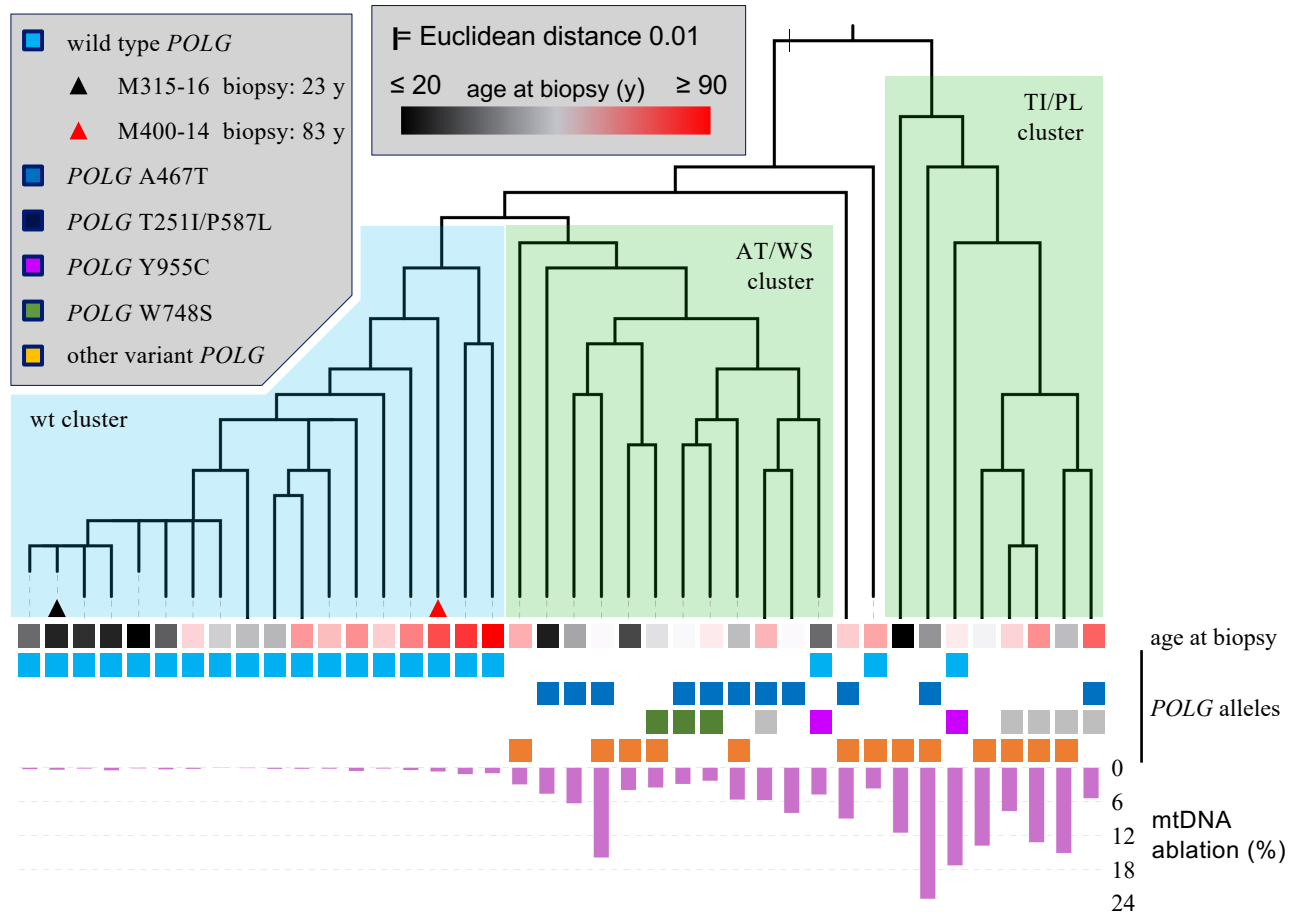
POLG W748S/R1096C:

- This patient is a 49 y.o. male with age of on-set at 25 yrs
- Diagnosed with PEO, ptosis, peripheral neuropathy, and epilepsy
- Has 16% COX negative muscle fibers and 5% ragged red fibers

Mito Deletion Mapping Results

- Over 700 million reads
- 74% of the mtDNA genomes contained a deletion
- 2.9 million deletions detected
- 24,360 unique deletions

MtDNA deletion clusters



Samples cluster by deletion pattern, WT control samples independently from POLG patient samples.

Lujan et al., 2020 ***Genome Biology***

What does the future hold for POLG- related disorder

More accurate and faster diagnosis

- Lots of published literature available for the clinicians, families and patients

- WGS and WES genome sequencing to quickly identify POLG and related disease mutation
  http://tools.niehs.nih.gov/polg/

- Sequencing mostly covered by heath insurance

What does the future hold for POLG- related disorder

Better disease models to develop therapies

- Cell based models
- Mouse models of POLG, POLG2 and Twinkle
- Zebra Fish models of POLG and POLG2 disease
- Organoids

Human Molecular Genetics, 2005, Vol. 14, No. 13 ***1775–1783***
doi:10.1093/hmg/ddi184
Advance Access published on May 11, 2005

Mitochondrial DNA polymerase gamma is essential for mammalian embryogenesis

Nicole Hance, Mats I. Ekstrand and Aleksandra Trifunovic*

Department of Medical Nutrition and Department of Biosciences at Novum, Karolinska Institute, Stockholm, Sweden

Received April 13, 2005; Revised and Accepted May 4, 2005

Human Molecular Genetics, 2013, Vol. 22, No. 5 ***1017–1025***
doi:10.1093/hmg/dds506
Advance Access published on November 29, 2012

Polg2 is essential for mammalian embryogenesis and is required for mtDNA maintenance

Margaret M. Humble[1], Matthew J. Young[1], Julie F. Foley[2], Arun R. Pandiri[3], Greg S. Travlos[4] and William C. Copeland[1,*]

What does the future hold for POLG- related disorder

Better disease models to develop therapies

- Cell based models
- Mouse models of POLG, POLG2 and Twinkle
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- Organoids

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ARTICLE OPEN

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Zebrafish *polg2* knock-out recapitulates human POLG-disorders; implications for drug treatment

Raquel Brañas Casas[1], Alessandro Zuppardo[2], Giovanni Risato[1,3], Alberto Dinarello[1,4], Rudy Celeghin[3], Camilla Fontana[1,5], Eleonora Grelloni[1], Alexandru Ionut Gilea[6], Carlo Viscomi[2], Andrea Rasola[2], Luisa Dalla Valle[1], Tiziana Lodi[6], Enrico Baruffini[6], Nicola Facchinello[7]✉, Francesco Argenton[1]✉ and Natascia Tiso[1]✉

RESEARCH ARTICLE

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Hallmark Molecular and Pathological Features of POLG Disease are Recapitulated in Cerebral Organoids

*Anbin Chen, Tsering Yangzom, Yu Hong, Bjørn Christian Lundberg, Gareth John Sullivan, Charalampos Tzoulis, Laurence A. Bindoff, and Kristina Xiao Liang**

What does the future hold for POLG- related disorder

Therapies in the works

- Antioxidant therapy
- Anti-seizure, anti-epileptic drugs
- Nucleotide therapy
- Metformin
- Repurposing drugs and identifying new drugs
- Gene therapy

Neuroscience 259 (2014) 142–154

NOVEL VITAMIN K ANALOGS SUPPRESS SEIZURES IN ZEBRAFISH AND MOUSE MODELS OF EPILEPSY

J. J. RAHN, J. E. BESTMAN, B. J. JOSEY, E. S. INKS, K. D. STACKLEY, C. E. ROGERS, C. J. CHOU * AND S. S. L. CHAN *

Department of Drug Discovery and Biomedical Sciences, South Carolina College of Pharmacy, Medical University of South Carolina, Charleston, SC 29425, USA

National Institute of Neurological Disorders and Stroke (NINDS) Anticonvulsant Screening Program. Compound 2h reduced seizures particularly well in the minimal clonic seizure (6 Hz) and corneal-kindled mouse models of epilepsy, with no observable toxicity. As VK3 affects mitochondrial function, we tested the effects of our compounds on mitochondrial respiration and ATP production in a mouse hippocampal cell line. We demonstrate that these com-

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frontiers | Frontiers in Cell and Developmental Biology

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Nucleoside supplements as treatments for mitochondrial DNA depletion syndrome

Eszter Dombi[1], Tony Marinaki[2], Paolo Spingardi[3], Val Millar[4], Nastasia Hadjichristou[5], Janet Carver[1], Iain G. Johnston[6,7], Carl Fratter[8] and Joanna Poulton[1]*

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RESEARCH ARTICLE

The FASEB Journal

Deoxyribonucleoside treatment rescues EtBr-induced mtDNA depletion in iPSC-derived neural stem cells with POLG mutations

Cecilie Katrin Kristiansen[1,2] | Jessica Furriol[3] | Anbin Chen[1,4] | Gareth John Sullivan[5,6,7] | Laurence A. Bindoff[1,8,9] | Kristina Xiao Liang[1,2]

[1]Department of Clinical Medicine, University of Bergen, Bergen, Norway

[2]Neuro-SysMed, Center of Excellence for Clinical Research in Neurological Diseases, Haukeland University Hospital, Bergen, Norway

What does the future hold for POLG- related disorder

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- Metformin
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frontiers in Cell and Developmental Biology

ORIGINAL RESEARCH
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Nicotinamide Riboside and Metformin Ameliorate Mitophagy Defect in Induced Pluripotent Stem Cell-Derived Astrocytes With *POLG* Mutations

OPEN ACCESS

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Andreas Hermann,

Anbin Chen[1,2,3,4], Cecilie Katrin Kristiansen[3,4], Yu Hong[3,4], Atefeh Kianian[3], Evandro Fei Fang[5,6], Gareth John Sullivan[7,8,9,10], Jian Wang[1,2,11], Xingang Li[1,2†], Laurence A. Bindoff[3,4*†] and Kristina Xiao Liang[3,4*†]*

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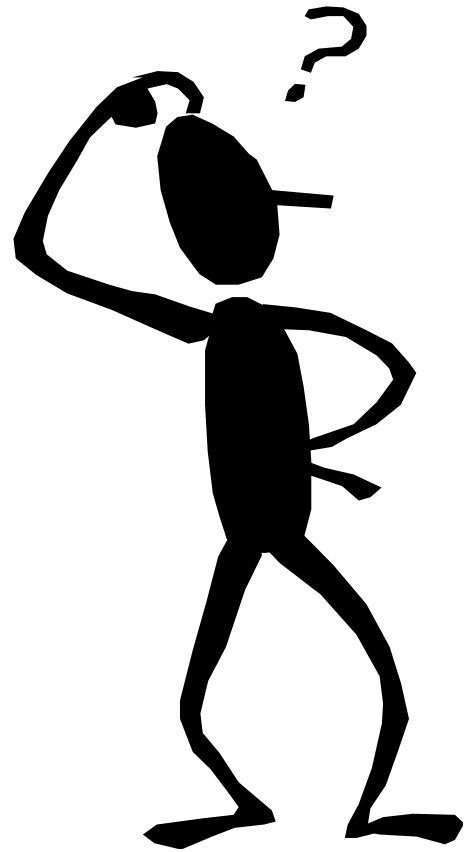

Questions