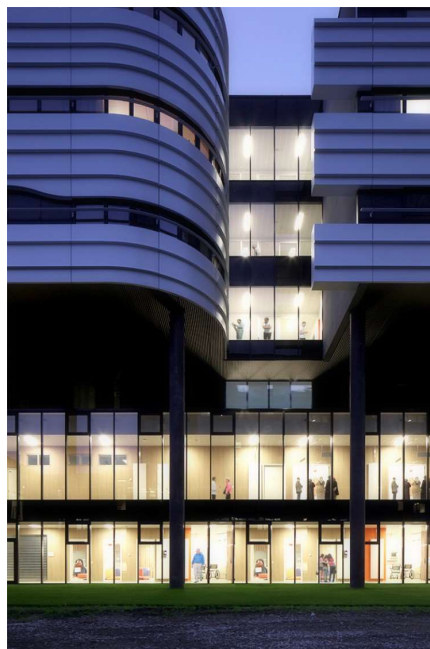
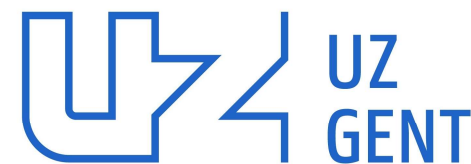




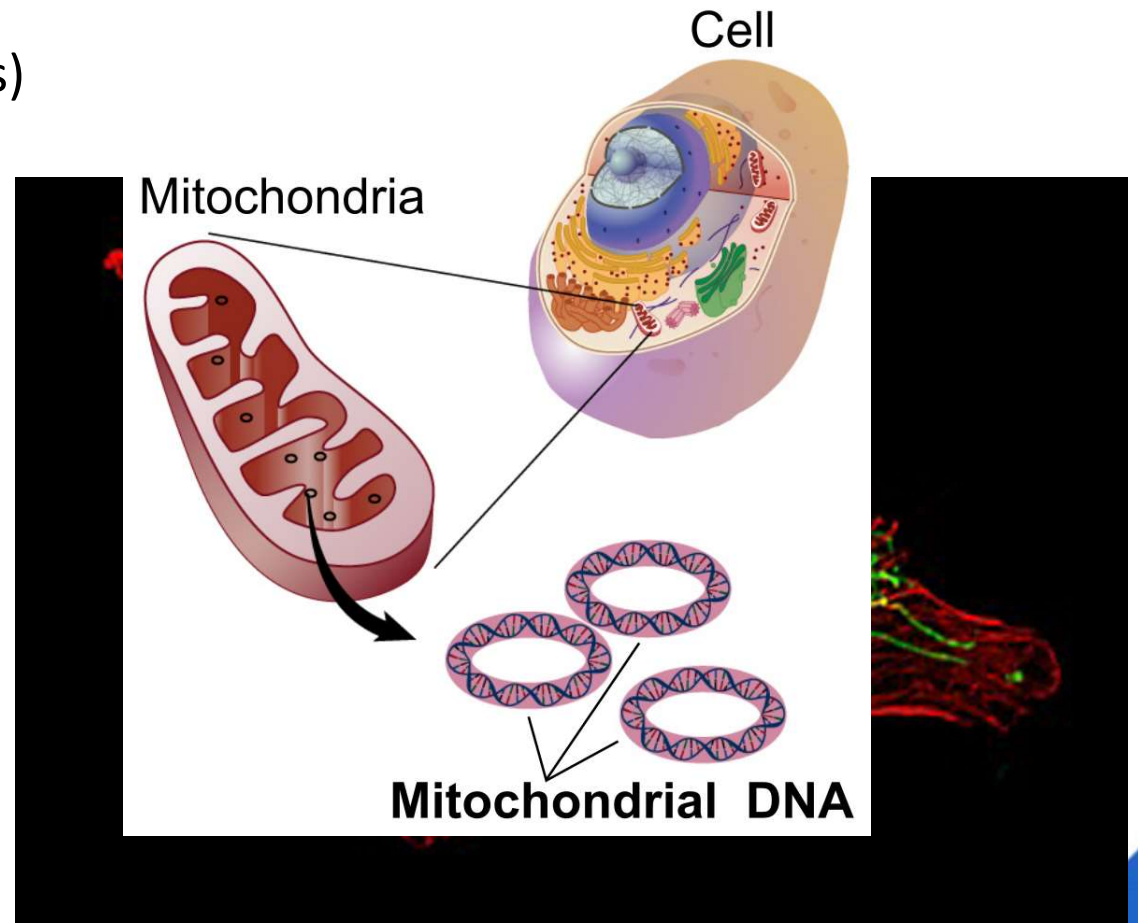
Mitochondrial Diseases

Arnaud Vanlander, M.D., PhD.



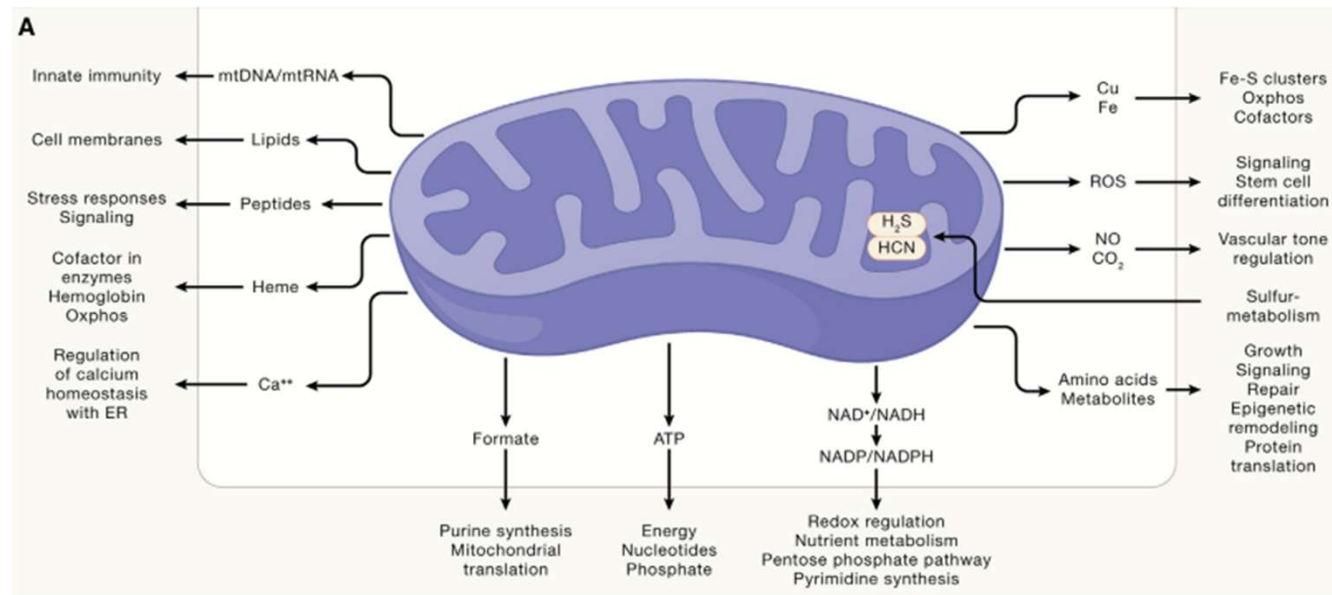
Mitochondria

- Present in all cells (except mature RBC's)
- Multiple copies/cell
- Dynamic network



Mitochondria - functions

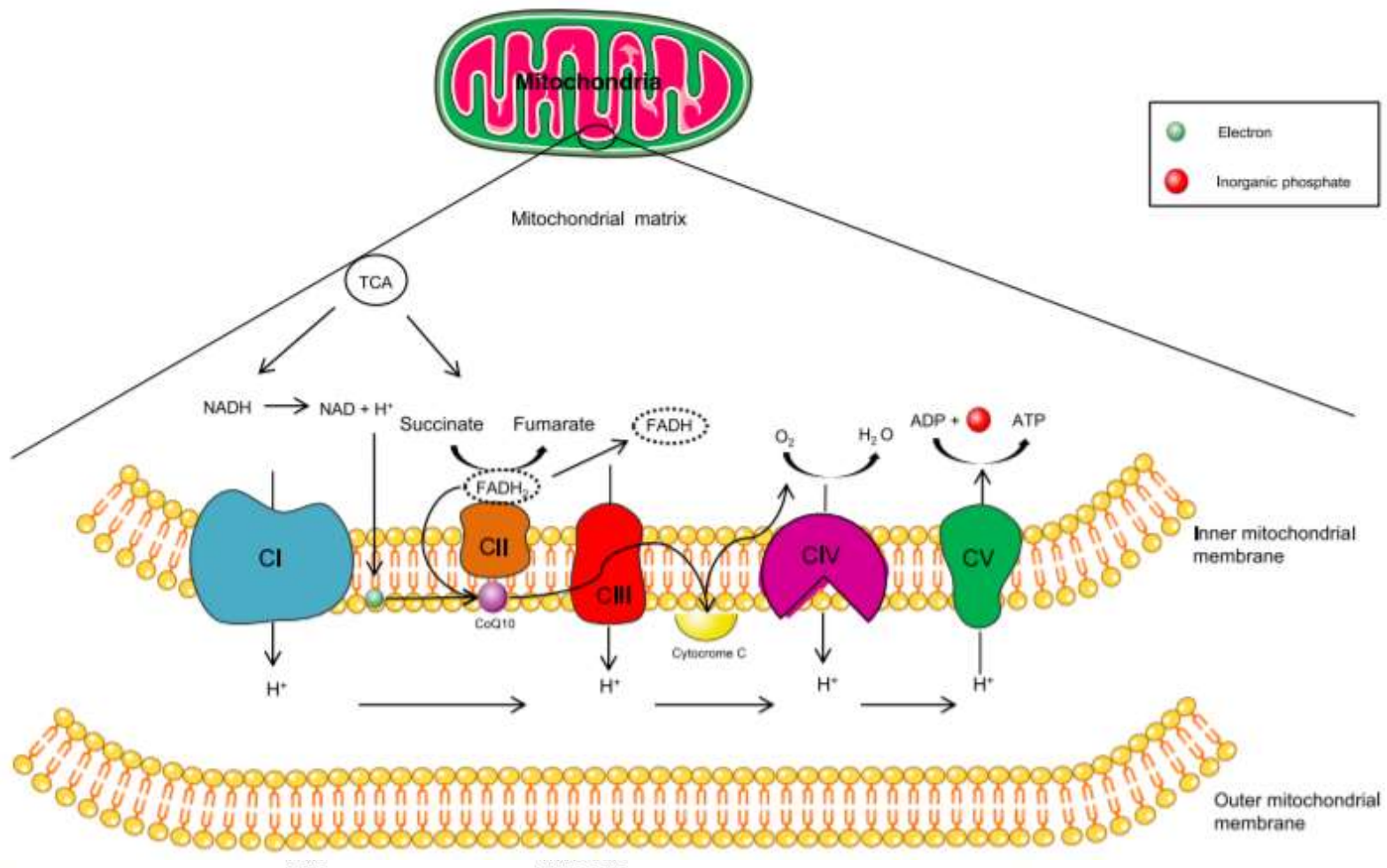
- Calcium homeostasis
- Apoptosis, ferroptosis
- Autophagy, cellular stress responses
- Different enzymatic pathways
 - (e. g. Krebs cycle, urea cycle, heme synthesis)
- ATP-production (Krebs cycle – OXPHOS)
- Redox balance



Primary mitochondrial diseases

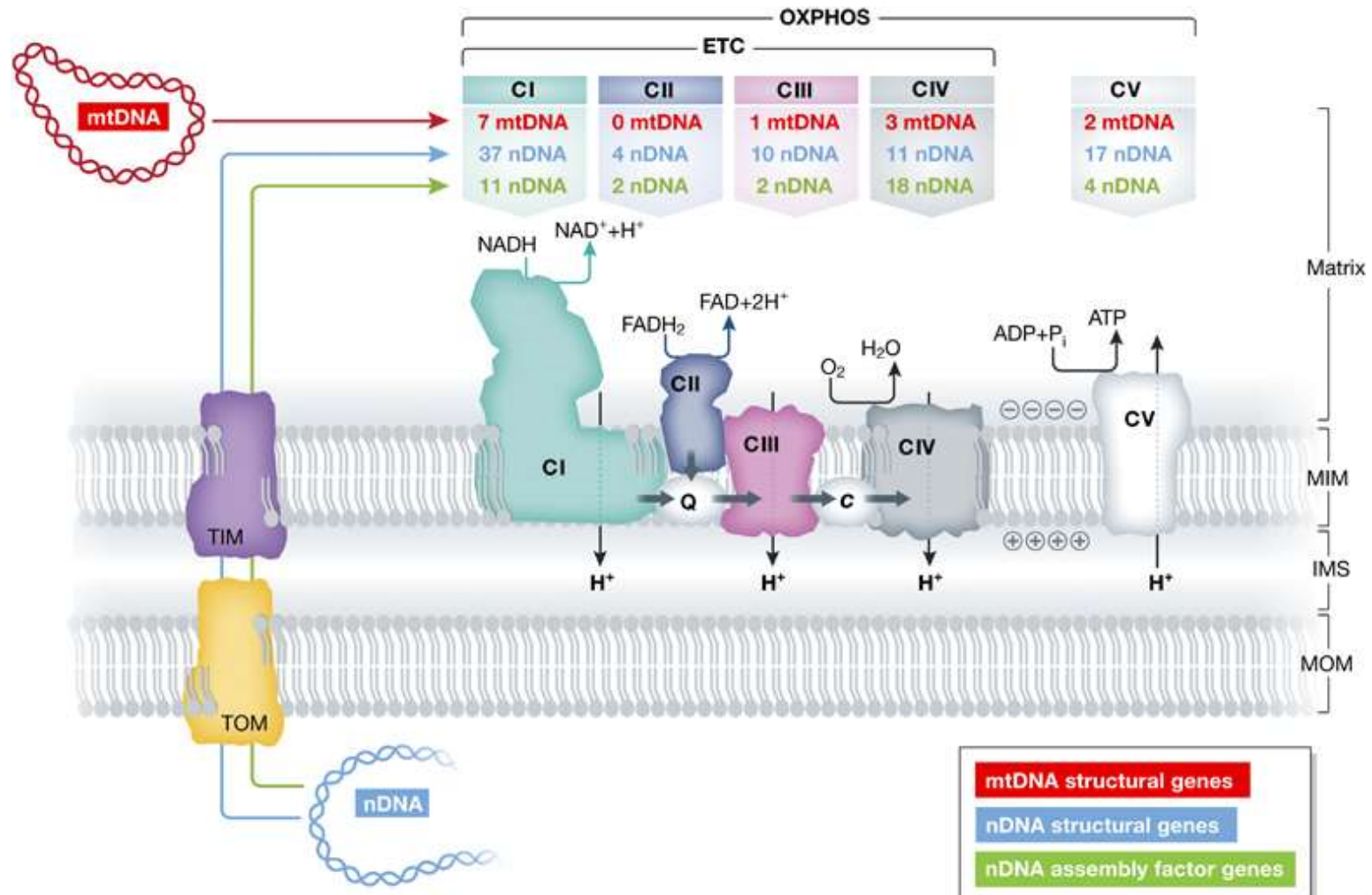
Mitochondria – ATP production

- Oxidative Phosphorylation (OXPHOS) (C I - V)



OXPHOS built up

- Functions thanks to the concerted action of two genomes



Mitochondrial diseases

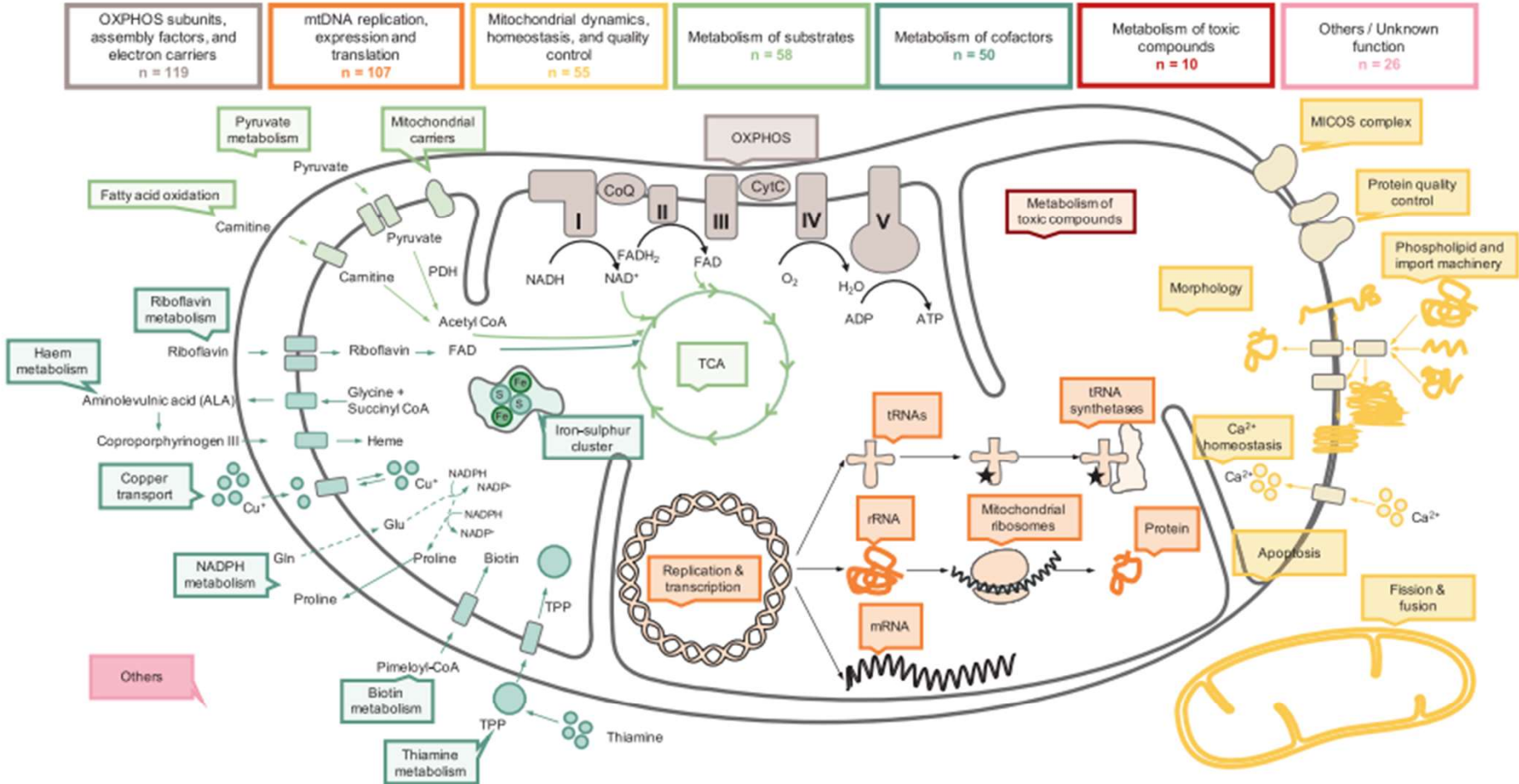
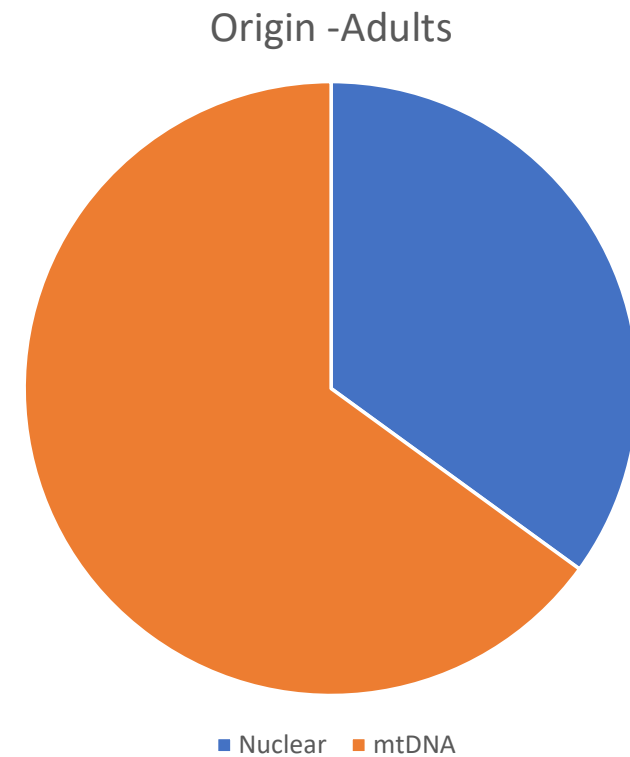
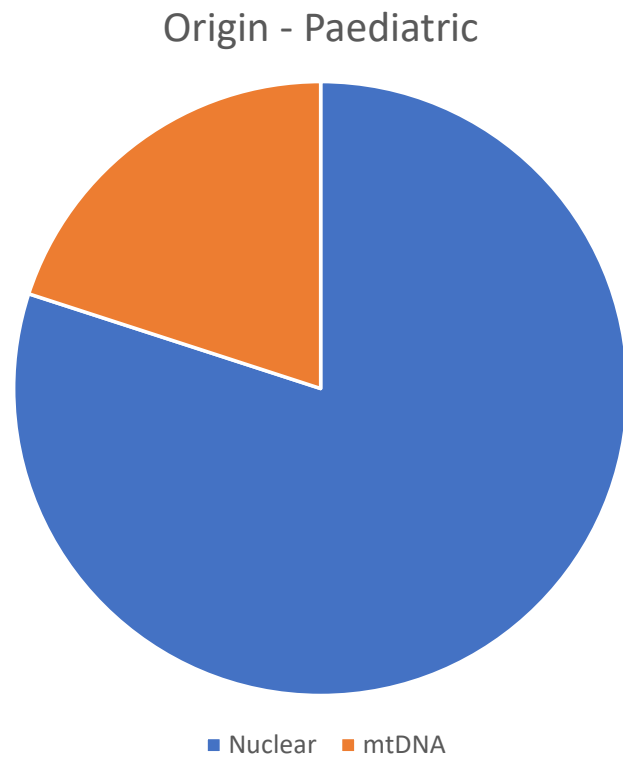


Fig. 10.1. Mitochondrion. Functional roles of mitochondria. The number of mitochondrial disease genes implicated in the functional subgroups is indicated.

Genetic origin of mitochondrial diseases

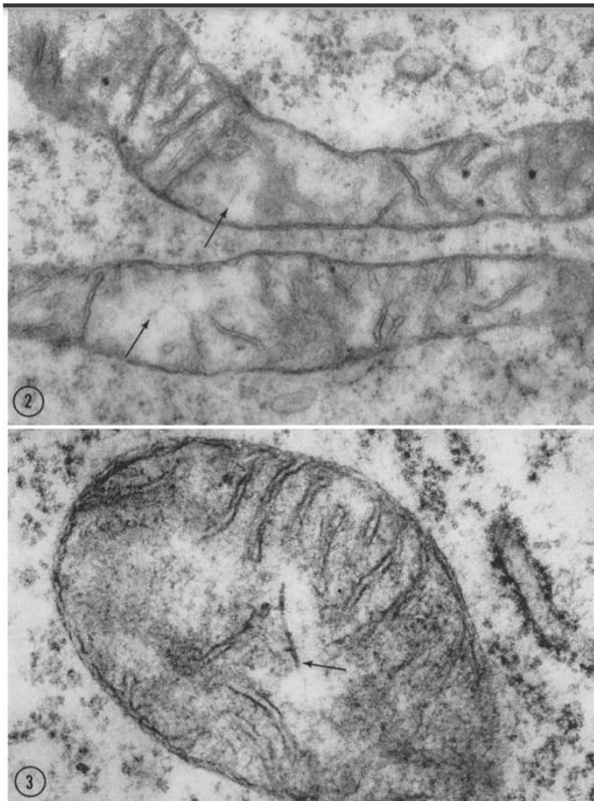


mtDNA

Discovered:

1963 (Nass and Nass, 1963)

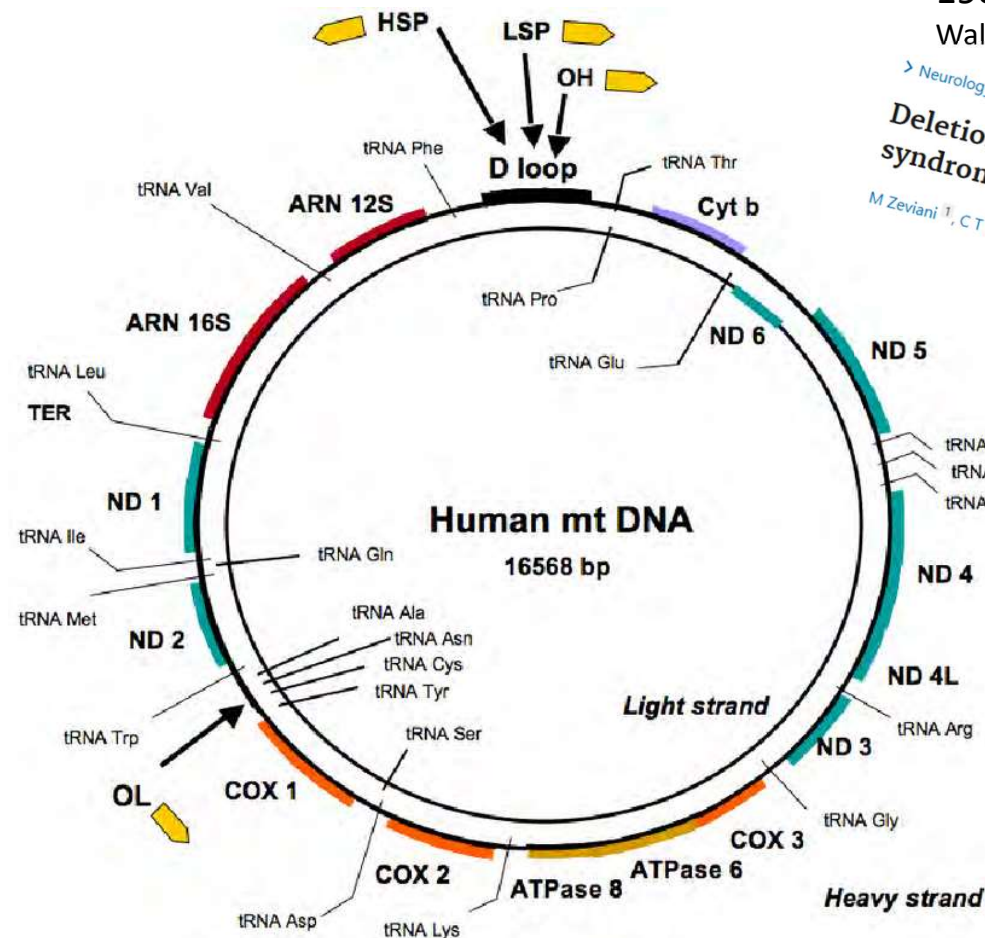
INTRAMITOCHONDRIAL FIBERS
WITH DNA CHARACTERISTICS



First alterations:

1988 (Zeviani et al., 1988; Holt et al., 1988;
Wallace et al., 1988)

> *Neurology*. 1988 Sep;38(9):1339-46. doi: 10.1212/wnl.38.9.1339.
Deletions of mitochondrial DNA in Kearns-Sayre syndrome
M Zeviani¹, C T Moraes, S DiMauro, H Nakase, E Bonilla, E A Schon, L P Rowland



Nuclear genes involved in mitochondrial functioning: Mitocarta 3.0

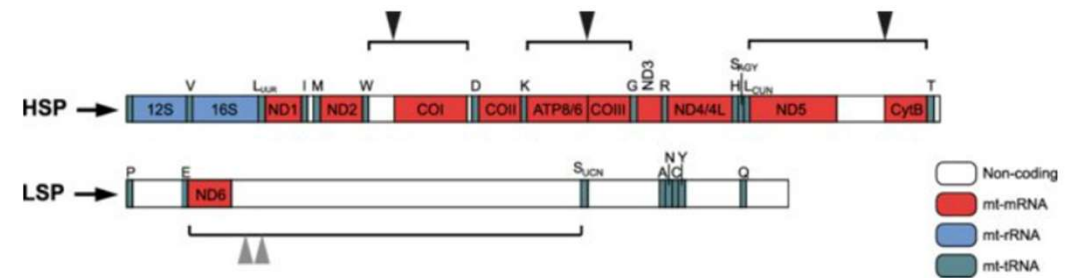
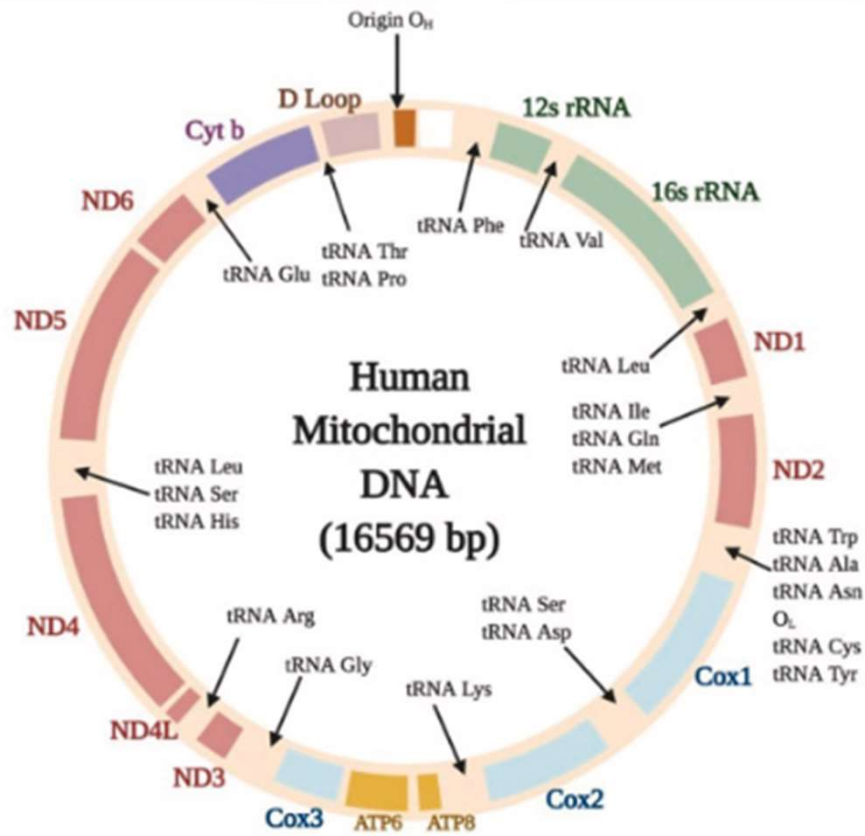
Human MitoCarta3.0: 1136 mitochondrial genes

The MitoCarta3.0 human inventory is a collection of 1136 nuclear and mtDNA genes encoding proteins with strong support of mitochondrial localization. This table provides a summary of evidence supporting mitochondrial localization, the protein distribution across 14 tissues, as well as annotation of biological pathways (based on manual literature review) and sub-compartment (based on annotator's "best guess" integrating sequence features, experimental data, literature, and pathway context; note all subunits of protein complexes are assigned the same compartment). The genes are ordered by strength of mitochondrial evidence. More complete information is available for download in file [Human MitoCarta3.0.xls](#). See also [MitoCarta3.0 home](#) for a description of the project and [MitoCarta3.0 documentation](#) for information on the columns below.

Symbol	Description	Synonyms	Maestro score	Evidence	Sub-compartment	MitoPathways	Tissues
CYC1	cytochrome c1	MC3DN6, UQCR4, P08574, gene:1537	43	literature, APEX IMS, APEX matrix, targetP signal, yeast mito homolog++, Rickettsial homolog, mito protein domain+, induction, coexpression++, MS/MS++	MIM	OXPHOS > Complex III > CIII subunits; Metabolism > Metals and cofactors > Heme-containing proteins; Metabolism > Electron carriers > Cytochromes; OXPHOS > OXPHOS subunits	all 14
SDHB	succinate dehydrogenase complex iron sulfur subunit B	CWS2, IP, PGL4, SDH, SDH1, SDH2, SDHIP, P21912, gene:6390	43	literature, APEX matrix, targetP signal+, yeast mito homolog, Rickettsial homolog, mito protein domain+, induction, coexpression++, MS/MS++	MIM	OXPHOS > Complex II > CII subunits; Metabolism > Carbohydrate metabolism > TCA cycle; Metabolism > Metals and cofactors > Fe-S-containing proteins; OXPHOS > OXPHOS subunits	all 14
COQ7	coenzyme Q7, hydroxylase	CAT5, CLK-1, CLK1, COQ10D8, Q99807, gene:10229	43	literature, targetP signal-, yeast mito homolog++, Rickettsial homolog, mito protein domain+, coexpression++, MS/MS++	MIM	Metabolism > Metals and cofactors > Coenzyme Q metabolism	all 14
SDHA	succinate dehydrogenase complex flavoprotein subunit A	CMD1GG, FP, PGL5, SDH1, SDH2, SDHF, P31040, gene:6389	42	literature, APEX matrix, targetP signal+, yeast mito homolog++, Rickettsial homolog, mito protein domain, induction, coexpression++, MS/MS++	MIM	OXPHOS > Complex II > CII subunits; Metabolism > Carbohydrate metabolism > TCA cycle; OXPHOS > OXPHOS subunits	all 14
UQCRC1	ubiquinol-cytochrome c reductase core protein 1	D3S3191, QCR1, UQCR1, P31930, gene:7384	42	literature, APEX matrix, targetP signal+, yeast mito homolog+, Rickettsial homolog, mito protein domain-, induction, coexpression++, MS/MS++	MIM	Protein import, sorting and homeostasis > Protein import and sorting > Preprotein cleavage; OXPHOS > Complex III > CIII subunits; OXPHOS > OXPHOS subunits	all 14
COQ5	coenzyme Q5, methyltransferase	Q5HYK3, gene:84274	42	APEX matrix, targetP signal, yeast mito homolog++, Rickettsial homolog, mito protein domain-, induction, coexpression++, MS/MS++	MIM	Metabolism > Metals and cofactors > Coenzyme Q metabolism	all 14
PDHA1	pyruvate dehydrogenase E1 subunit alpha 1	PDHA, PDHAD, PDHCE1A, PHE1A, P08559, gene:5160	42	literature, APEX matrix, targetP signal+, yeast mito homolog+, Rickettsial homolog, mito protein domain-, induction, coexpression++, MS/MS++	Matrix	Metabolism > Carbohydrate metabolism > Pyruvate metabolism	all 14
COQ9	coenzyme Q9	C16orf49, COQ10D5, O75208, gene:57017	42	APEX matrix, targetP signal+, yeast mito homolog++, Rickettsial homolog, mito protein domain-, induction, coexpression, MS/MS++	MIM	Metabolism > Metals and cofactors > Coenzyme Q metabolism	all 14
MRPL12	mitochondrial ribosomal protein L12	5c5-2, L12mt, MRP-L31/34, MRPL7, MRPL7/L12, RPML12, P52815, gene:6182	42	literature, targetP signal-, yeast mito homolog++, Rickettsial homolog, mito protein domain, induction, coexpression++, MS/MS++	Matrix	Mitochondrial central dogma > mtRNA metabolism > Transcription; Mitochondrial central dogma > Translation > Mitochondrial ribosome	all 14
ATP5F1D	ATP synthase F1 subunit delta	ATP5D, MC5DN5, P30049, gene:513	42	literature, APEX matrix, targetP signal, yeast mito homolog++, Rickettsial homolog, mito protein domain-, induction, coexpression++, MS/MS+	MIM	OXPHOS > Complex V > CV subunits; OXPHOS > OXPHOS subunits	all 14
COX5A	cytochrome c oxidase subunit 5A	COX, COX-VA, VA, P20674, gene:9377	42	literature, APEX IMS, APEX matrix, targetP signal-, yeast mito homolog++, mito protein domain-, induction, coexpression++, MS/MS++	MIM	OXPHOS > Complex IV > CIV subunits; OXPHOS > OXPHOS subunits	all 14
ISCA2	iron-sulfur cluster assembly 2	HBLD1, ISA2, MMDS4, c14_5557, Q86U28, gene:122961	42	APEX matrix, targetP signal+, yeast mito homolog++, Rickettsial homolog, mito protein domain-, induction, coexpression, MS/MS++	Matrix	Metabolism > Metals and cofactors > Fe-S cluster biosynthesis; Metabolism > Metals and cofactors > Fe-S-containing proteins	all 14
PMPCB	peptidase, mitochondrial processing subunit beta	Beta-MPP, MPP11, MPPB, MPPP52, P-52, O75439, gene:9512	41	literature, APEX matrix, targetP signal+, yeast mito homolog+, Rickettsial homolog, mito protein domain-, induction, coexpression++, MS/MS++	Matrix	Protein import, sorting and homeostasis > Protein import and sorting > Preprotein cleavage; Protein import, sorting and homeostasis > Protein homeostasis > Proteases	all 14
UQCRCF1	ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide 1	MC3DN10, R1P1, RIS1, RISP, UQCR5, P47985, gene:7386	40	literature, APEX matrix, targetP signal, yeast mito homolog++, Rickettsial homolog, mito protein domain-, coexpression++, MS/MS++	MIM	OXPHOS > Complex III > CIII subunits; Metabolism > Metals and cofactors > Fe-S-containing proteins; OXPHOS > OXPHOS subunits	all 14
ATP5F1A	ATP synthase F1 subunit alpha	ATP5A, ATP5A1, ATP5AL2, ATPM, COXPD22, HEL-S-123m, MC5DN4, MOM2, OMR, ORM, hATP1, P25705, gene:498	40	literature, APEX matrix, targetP signal+, yeast mito homolog++, Rickettsial homolog, mito protein domain, induction, coexpression++, MS/MS++	MIM	OXPHOS > Complex V > CV subunits; OXPHOS > OXPHOS subunits	all 14

1. OXPHOS subunits, assembly factors, and electron carriers			2. mtDNA replication, expression and translation			3. Mitochondrial dynamics, homeostasis, and quality control			4. Metabolism of substrates			5. Metabolism of cofactors		
CI subunit	CII subunit	CIV subunit	tRNAs	tRNA synthetases	RNA processing	Morphology	Quality control	Fission	Mitochondrial carriers	Fatty acid oxidation	Redox carriers	Haem biosynthesis	Iron-sulphur cluster biosynthesis	Lipoic acid biosynthesis
DNAJC30	SDHA	COX4I1	MT-TA	AARS2	ELAC2	MIEF2	AFG3L2	DNM1L	MPC1	ACADM	GOT2	ABCB6	ABC7	DLD*
MT-ND1	SDHB	COX4I2	MT-TC	CARS2	ERAL1	MSTO1	ATAD3A	GDAP1	SLC25A3	ACADS	MDH1	ALAS2	ABC7	LIAS
MT-ND2	SDHC	COX5A	MT-TD	DARS2	GTPBP3	OPA1	CLPB	MFF	SLC25A4	ACADSB	SLC25A1	COX10*	BOLA3	LIP1
MT-ND3	SDHD	COX6A1	MT-TE	EARS2	HSD17B10	YME1L1	CLPP	SLC25A46*	SLC25A10	ACADVL	SLC25A13	COX15*	FDX1L	LIP2
MT-ND4	CII assembly factors	COX6A2	MT-TF	FARS2	LRPPRC	Phospholipid and import machinery	CLPX	STAT2	SLC25A11	CPT1A	Tricarboxylic acid cycle	HCCS*	FXN	MECR
MT-ND4L		COX6B1	MT-TG	GARS	MRM2		HSPA9	Fusion	SLC25A12	CPT2		PPOX	GLRX5	
MT-ND5		COX7B	MT-TI	GATB	MTO1		HSPE1	MFN2	SLC25A15	CRAT		SFXN4	HSCB	
MT-ND6	SDHAF1	MT-CO1	MT-TK	GATC	MTPAP	Apoptosis defect	LONP1	NME3	SLC25A21	ETFA	Anaplerosis	SLC25A38	IBA57	Riboflavin metabolism
NDUFA1	SDHAF2	MT-CO2	MT-TL1	HARS2	NSUN3		MIPEP	Ca2+ homeostasis	SLC25A22	ETFB		SLC25A32	ISCA1	FLAD1
NDUFA10	CIII subunit	MT-CO3	MT-TL2	IARS2	PDE12		PFKP		SLC25A24	ETFDH		SLC25A33	ISCA2	SLC25A32
NDUFA12		NDUFA4	MT-TM	KARS	PNPT1	Translation regulation	PRORP		SLC25A26	FA2H	Ketone bodies	SLC25A34	ISCU	SLC25A32
NDUFA13			MT-TN	LARS2	PRORP		PUS1			FA2H		SLC25A35	LYRM4	SLC25A32
NDUFA2	CYC1	CIV assembly factors	MT-TP	MARS2	THG1L		TRMT5			SLC25A26	FA2H	Anaplerosis	SLC25A36	NFS1
NDUFA6	MT-CYB		MT-TQ	MTFMT	TRMT5	Nucleotide pool maintenance	TRMT5			FA2H	SLC25A37		NFS1	SLC25A32
NDUFA8	UCSRB		MT-TS1	NARS2	TRMT5		TRMT5			FA2H	SLC25A38		NFS1	SLC25A32
NDUFA9	UQCRC2	CEP89	MT-TS2	PARS2	TRMT5		TRMT5			FA2H	SLC25A39	NFS1	SLC25A32	
NDUFB10	UQCRCF1	COA3	MT-TT	QRS1	TRMT5		TRMT5			FA2H	SLC25A40	NFS1	SLC25A32	
NDUFB3	UQCRH	COA5	MT-TV	RARS2	TRMT5		TRMT5			FA2H	SLC25A41	NFS1	SLC25A32	
NDUFB7	UQCRCQ	COA6*	MT-TW	SARS2	TRMT5		TRMT5			FA2H	SLC25A42	NFS1	SLC25A32	
NDUFB8	CIII assembly factors	COA7	MT-TY	TARS2	TRMT5	DNA repair	TRMT5			FA2H	Anaplerosis	SLC25A43	NFS1	SLC25A32
NDUFB9		COX10*		WARS2	TRMT5		TRMT5			FA2H		SLC25A44	NFS1	SLC25A32
NDUFC2		COX14		YARS2	TRMT5		TRMT5			FA2H		SLC25A45	NFS1	SLC25A32
NDUFS1	BCS1L	COX15*				DNA repair	TRMT5			FA2H	Anaplerosis	SLC25A46	NFS1	SLC25A32
NDUFS2	LYRM7	COX20					TRMT5			FA2H		SLC25A47	NFS1	SLC25A32
NDUFS3	TTC19	FASTKD2					TRMT5			FA2H		SLC25A48	NFS1	SLC25A32
NDUFS4	UQC2	OXA1L*				TRMT5			FA2H	SLC25A49		NFS1	SLC25A32	
NDUFS6	UQC3	PET100				TRMT5			FA2H	SLC25A50		NFS1	SLC25A32	
NDUFS7		PET117				TRMT5			FA2H	SLC25A51		NFS1	SLC25A32	
NDUFS8		SCO1*				DNA repair	TRMT5			FA2H		SLC25A52	NFS1	SLC25A32
NDUFS9	Coenzyme Q10	SCO2*					TRMT5			FA2H		SLC25A53	NFS1	SLC25A32
NDUFV1		POLG					TRMT5			FA2H		SLC25A54	NFS1	SLC25A32
NDUFV2		POLG2				TRMT5			FA2H	SLC25A55		NFS1	SLC25A32	
		POLRMT				DNA repair	TRMT5			FA2H		SLC25A56	NFS1	SLC25A32
		RNASEH1					TRMT5			FA2H		SLC25A57	NFS1	SLC25A32
		SSBP1					TRMT5			FA2H		SLC25A58	NFS1	SLC25A32
		TFAM				DNA repair	TRMT5			FA2H		SLC25A59	NFS1	SLC25A32
		TOP3A					TRMT5			FA2H		SLC25A60	NFS1	SLC25A32
		TWNK					TRMT5			FA2H		SLC25A61	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A62	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A63	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A64	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A65	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A66	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A67	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A68	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A69	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A70	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A71	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A72	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A73	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A74	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A75	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A76	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A77	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A78	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A79	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A80	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A81	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A82	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A83	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A84	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A85	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A86	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A87	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A88	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A89	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A90	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A91	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A92	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A93	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A94	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A95	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A96	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A97	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A98	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A99	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A100	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A101	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A102	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A103	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A104	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A105	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A106	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A107	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A108	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A109	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A110	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A111	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A112	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A113	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A114	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A115	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A116	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A117	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A118	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A119	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A120	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A121	NFS1	SLC25A32
						DNA repair	TRMT5			FA2H		SLC25A122	NFS1	SLC25A32
							TRMT5			FA2H		SLC25A123	NFS1	SLC25A32
							TRMT5			FA2H	SLC25A124	NFS1	SLC25A32	
						DNA repair	TRMT5			FA2H	SLC25A125	NFS1	SLC25A32	
							TRMT5			FA2H	SLC25A126	NFS1	SLC25A32	
							TRMT5			FA2H	SLC25A127	NFS1	SLC25A32	
						DNA repair	TRMT5			FA2H	SLC25A128	NFS1	SLC25A32	
							TRMT5			FA2H	SLC25A129	NFS1	SLC25A32	
							TRMT5			FA2H	SLC25A130	NFS1	SLC25A32	
						DNA repair	TRMT5			FA2H	SLC25A131	NFS1	SLC25A32	
							TRMT5			FA2H	SLC25A132	NFS1	SLC25A32	
							TRMT5			FA2H	SLC25A133	NFS1	SLC25A32	
						DNA repair	TRMT5			FA2H	SLC25A134	NFS1	SLC25A32	
							TRMT5			FA2H	SLC25A135	NFS1	SLC25A32	
							TRMT5			FA2H	SLC25A136	NFS1	SLC25A32	
						DNA repair	TRMT5			FA2H	SLC25A137	NFS1	SLC25A32	
							TRMT5			FA2H	SLC25A138	NFS1	SLC25A32	
							TRMT5			FA2H	SLC25A139	NFS1	SLC25A32	
						DNA repair	TRMT5			FA2H	SLC25A140	NFS1	SLC25A32	
							TRMT5			FA2H	SLC25A141	NFS1	SLC25A32	
							TRMT5			FA2H	SLC25A142	NFS1	SLC25A32	
						DNA repair	TRMT5			FA2H	SLC25A143	NFS1	SLC25A32	
							TRMT5			FA2H	SLC25A144	NFS1	SLC25A32	

mtDNA: particularities



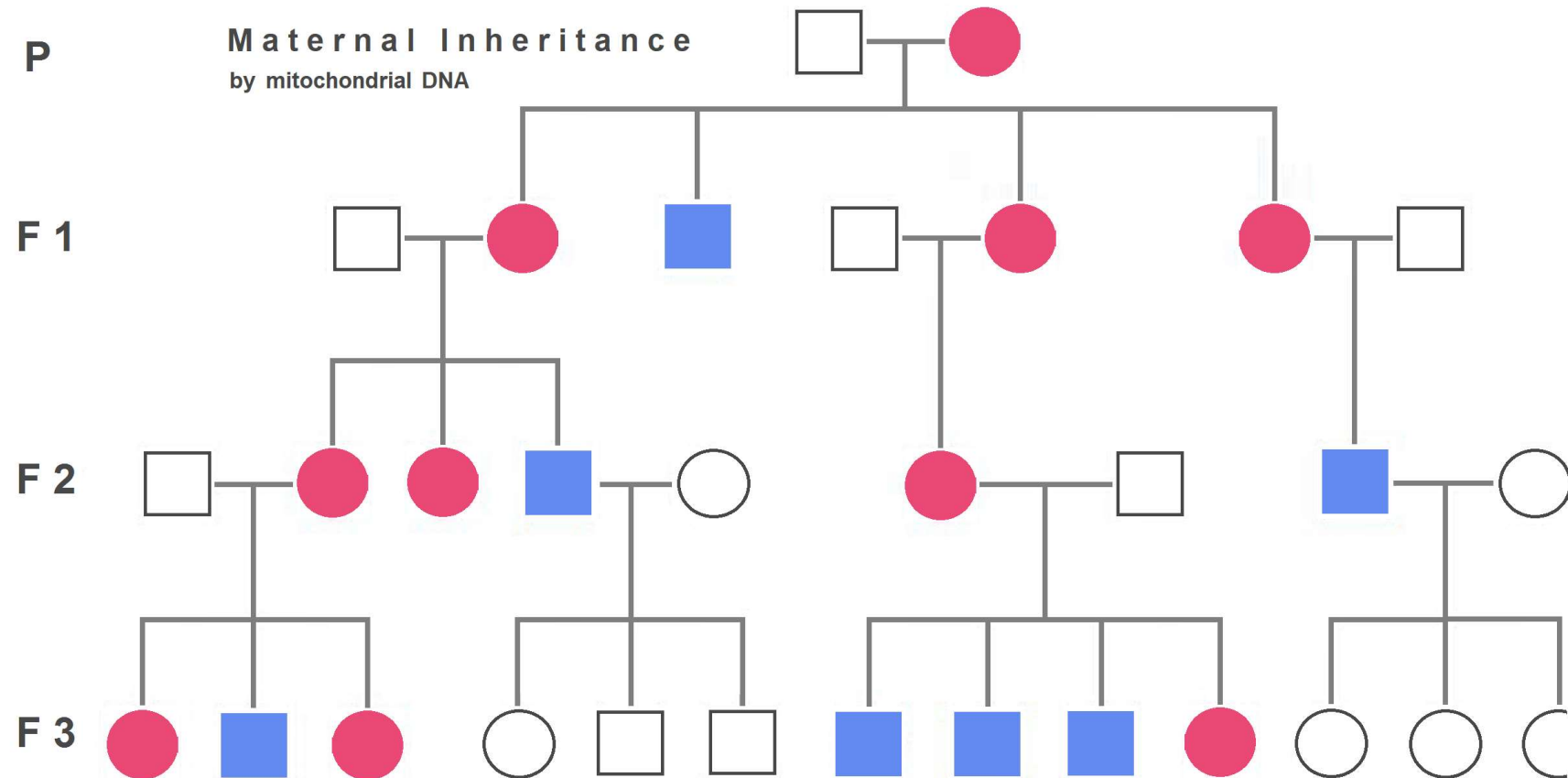
Particularities for mtDNA related disorders

- Particular genetic defects: Point mutations, Deletion(s), Depletion
- Inheritance
- Heteroplasmy
- Tissue specific genotype
- Bottleneck phenomenon



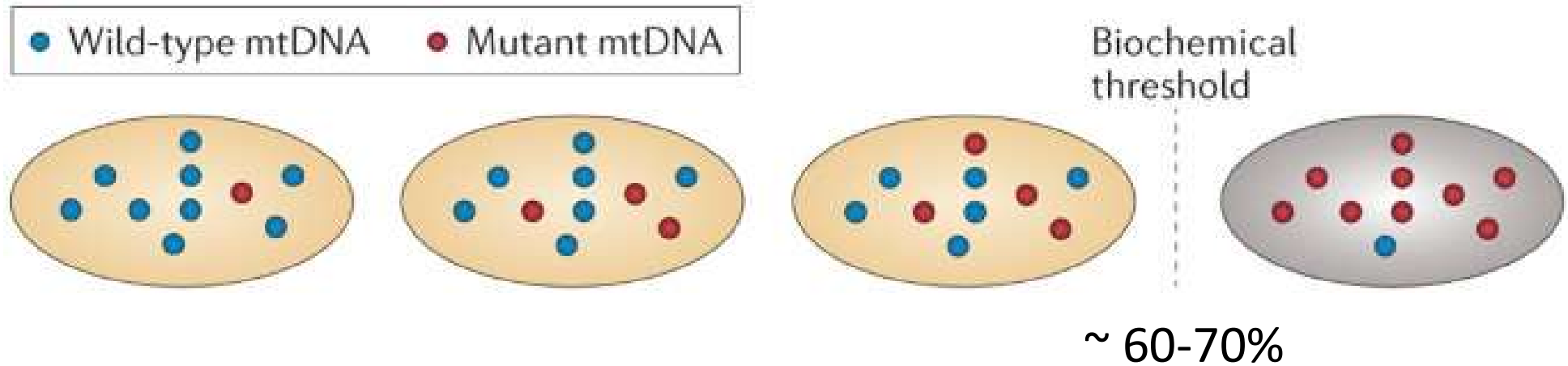
Particularities

- Maternal inheritance for mtDNA



Particularities

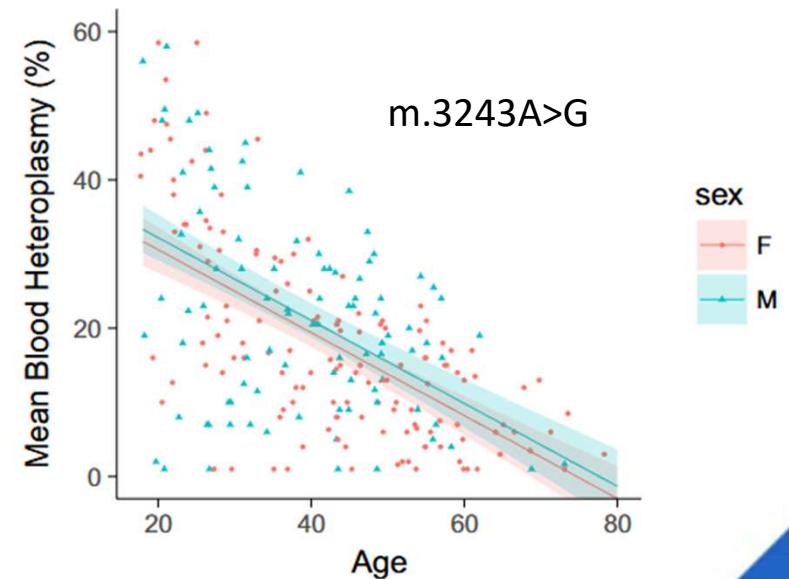
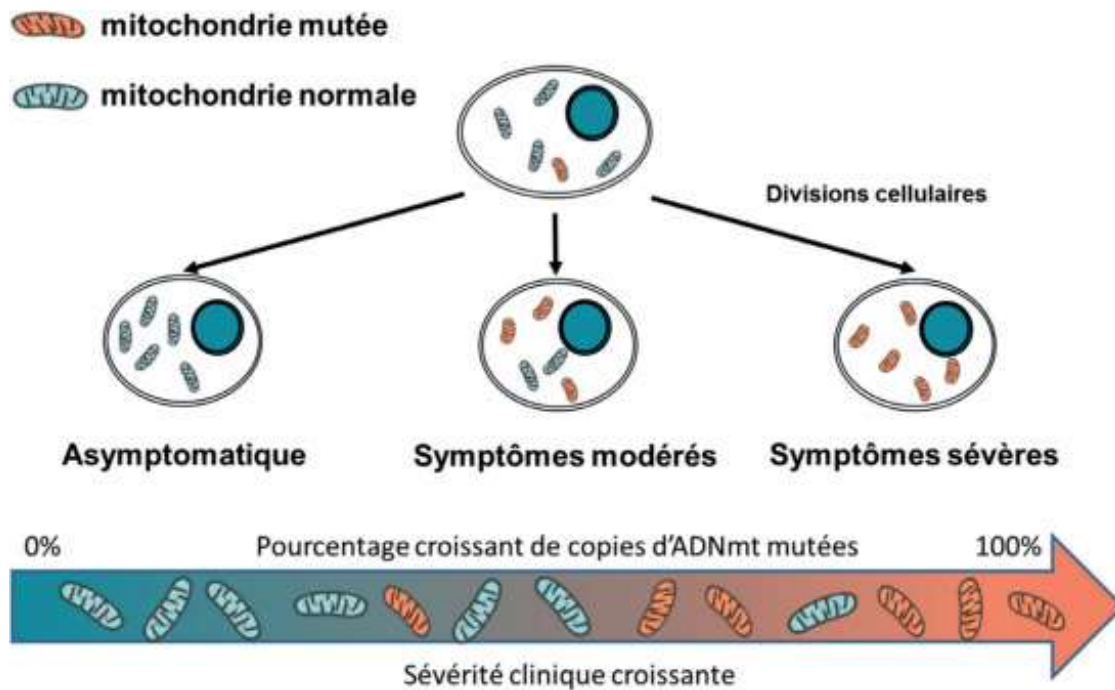
- Homoplasmy - heteroplasmy



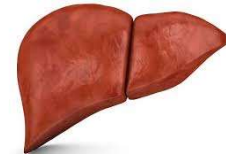
Heteroplasmy

Variability:

- tissue
- time

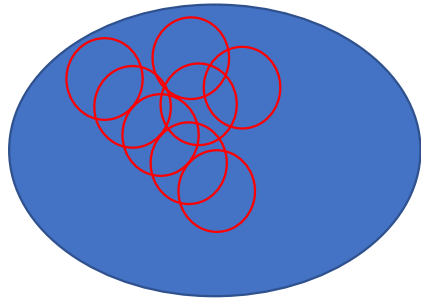


Heteroplasmy – tissue specificity

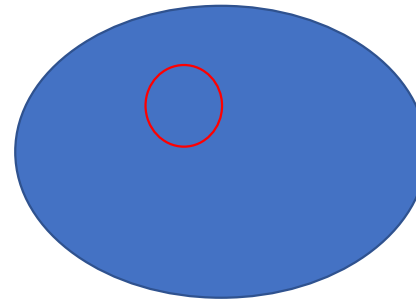


Importance for diagnostics: Think of relevance of mtDNA diagnostics in leukocytes?

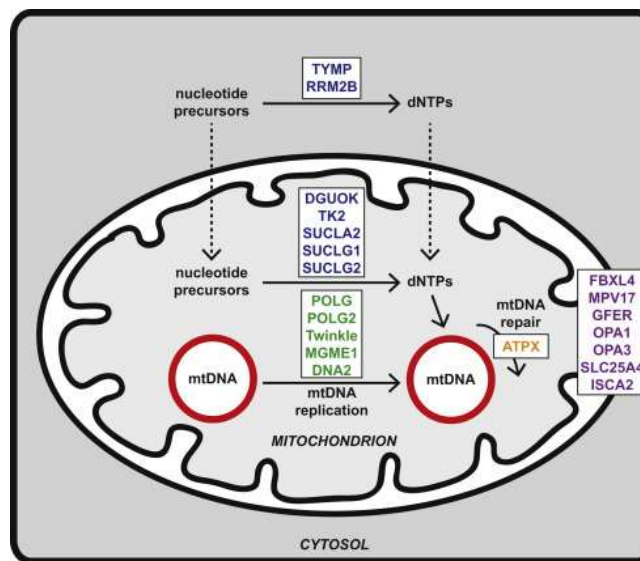
Depletion



Normal # mtDNA copies

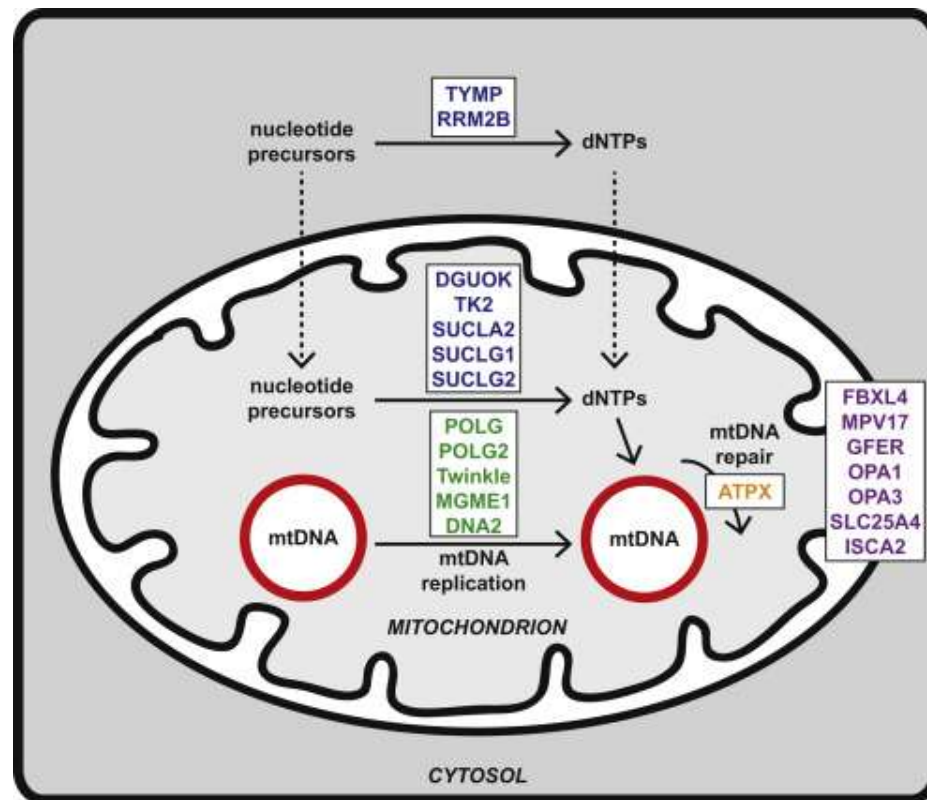


mtDNA depletion



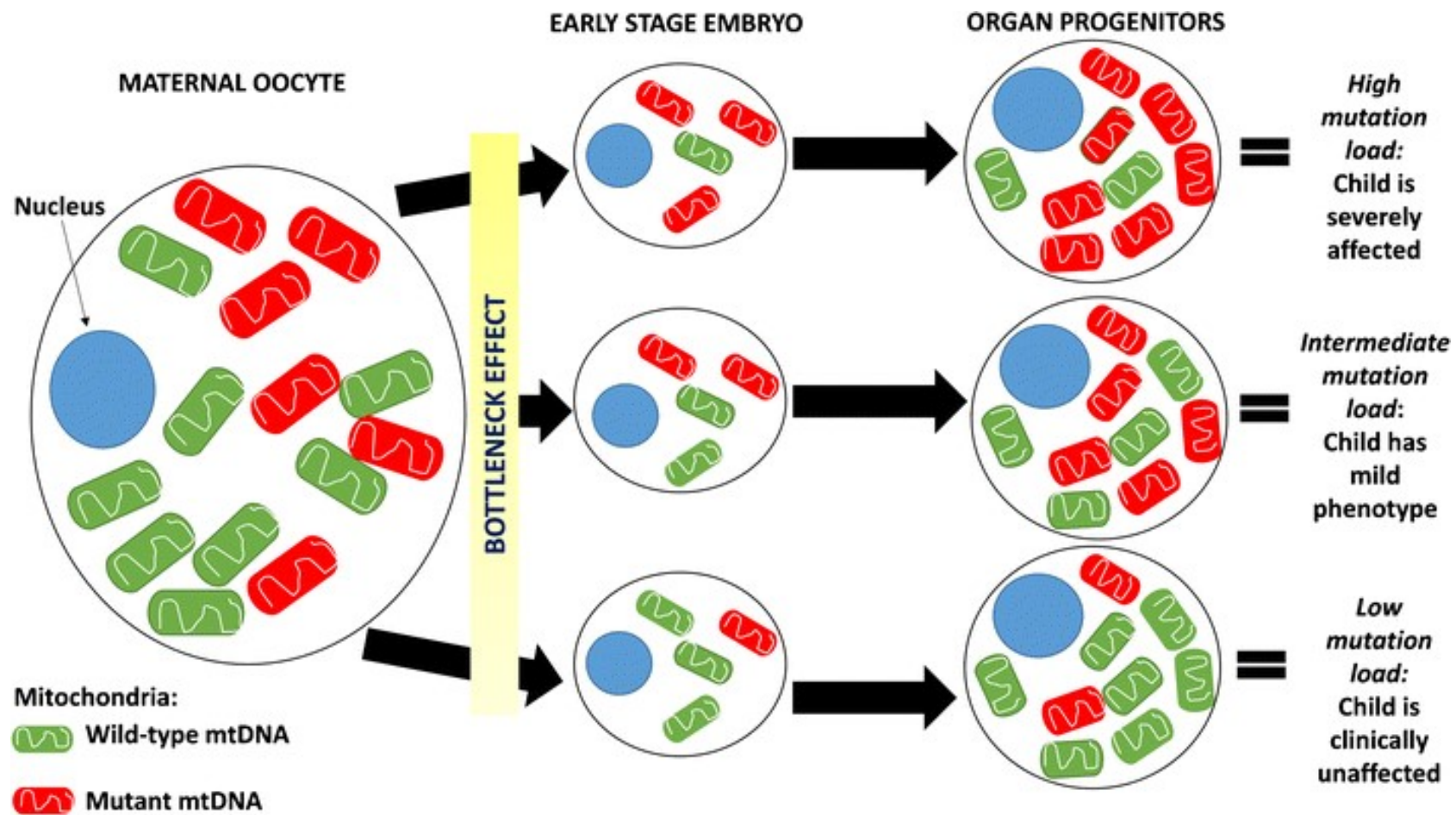
Depletion associated genes

All nuclearly encoded

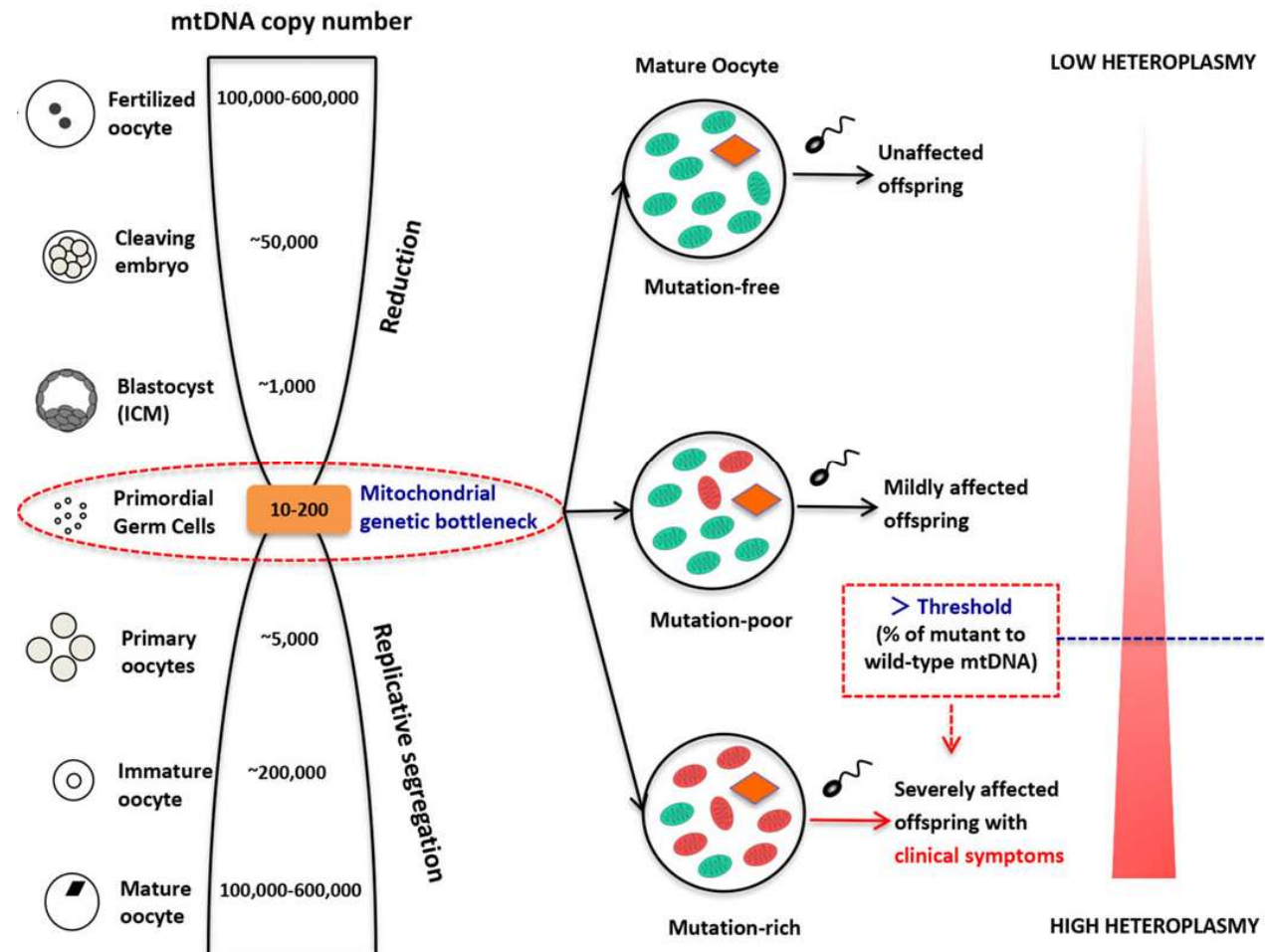


Particularities

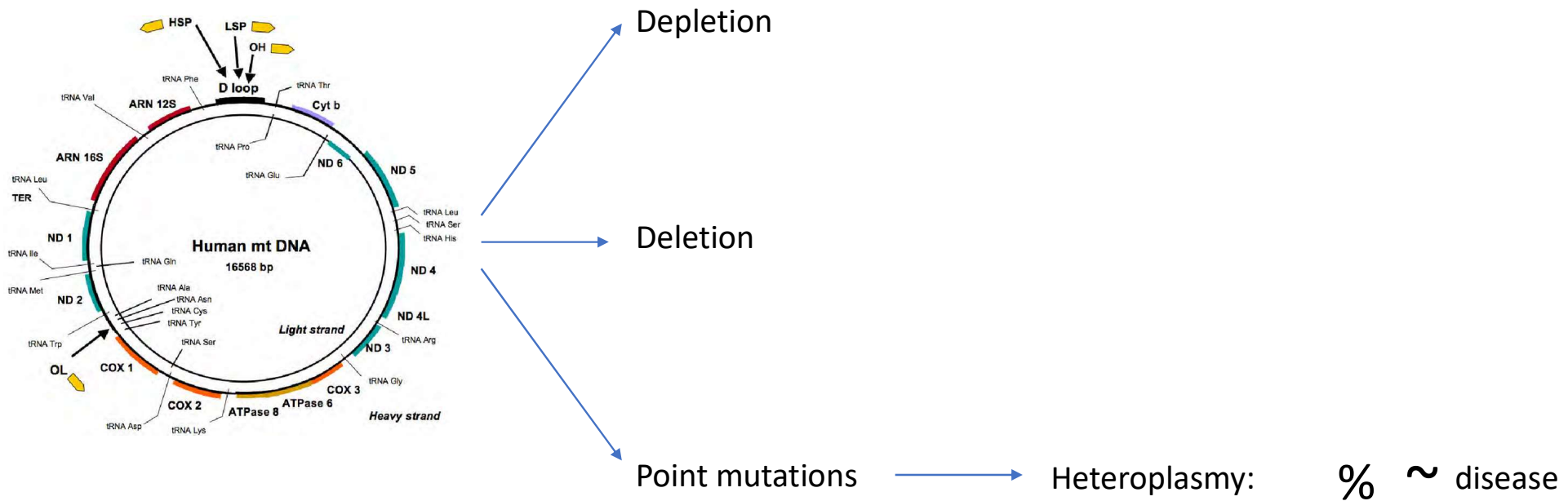
- Bottleneck phenomenon



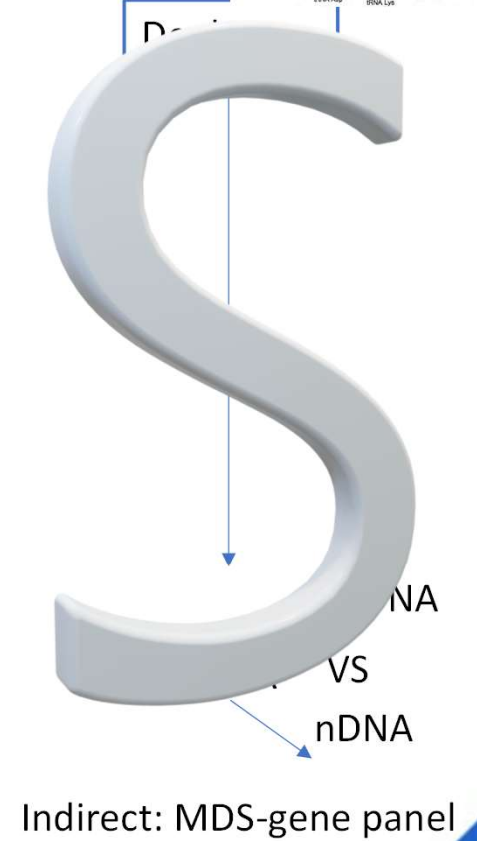
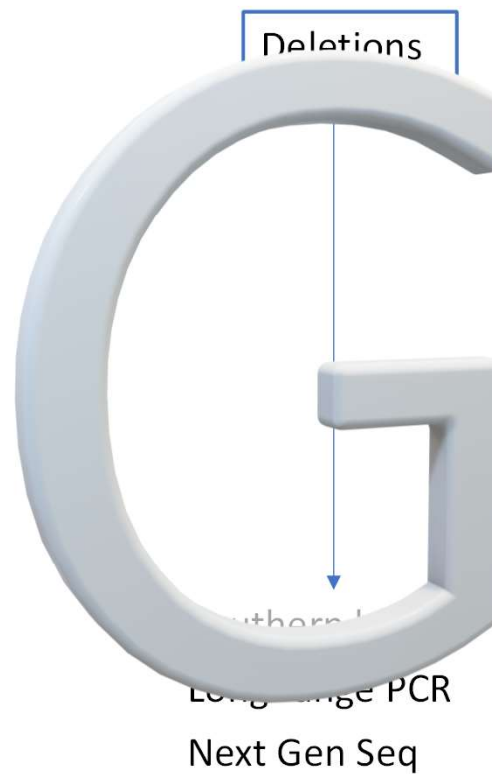
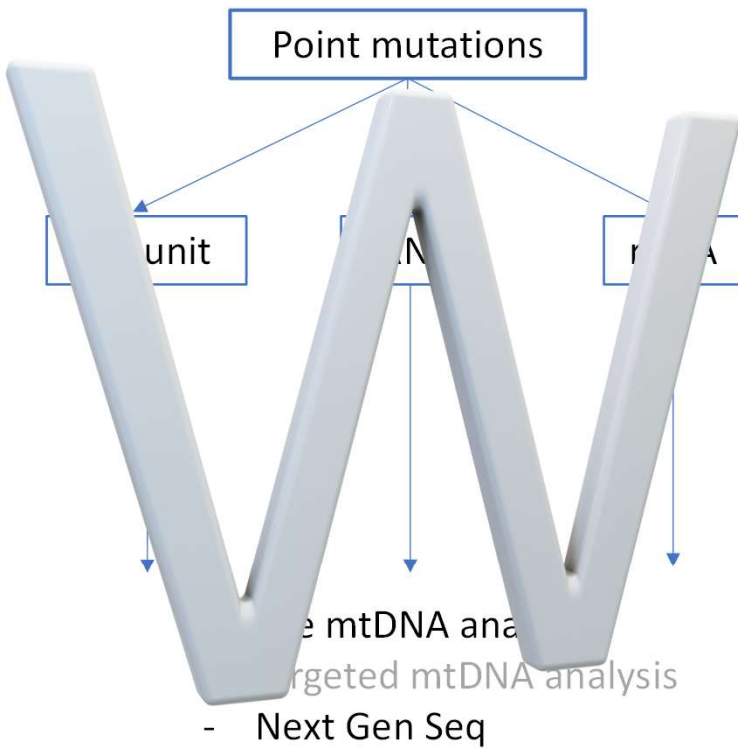
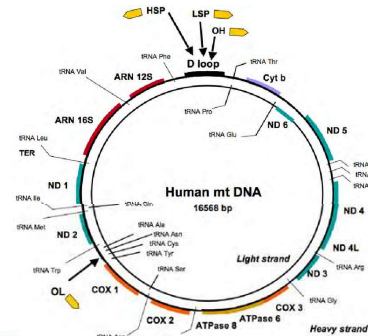
Bottleneck phenomenon



mtDNA related genetic defects



mtDNA alterations: detection techniques

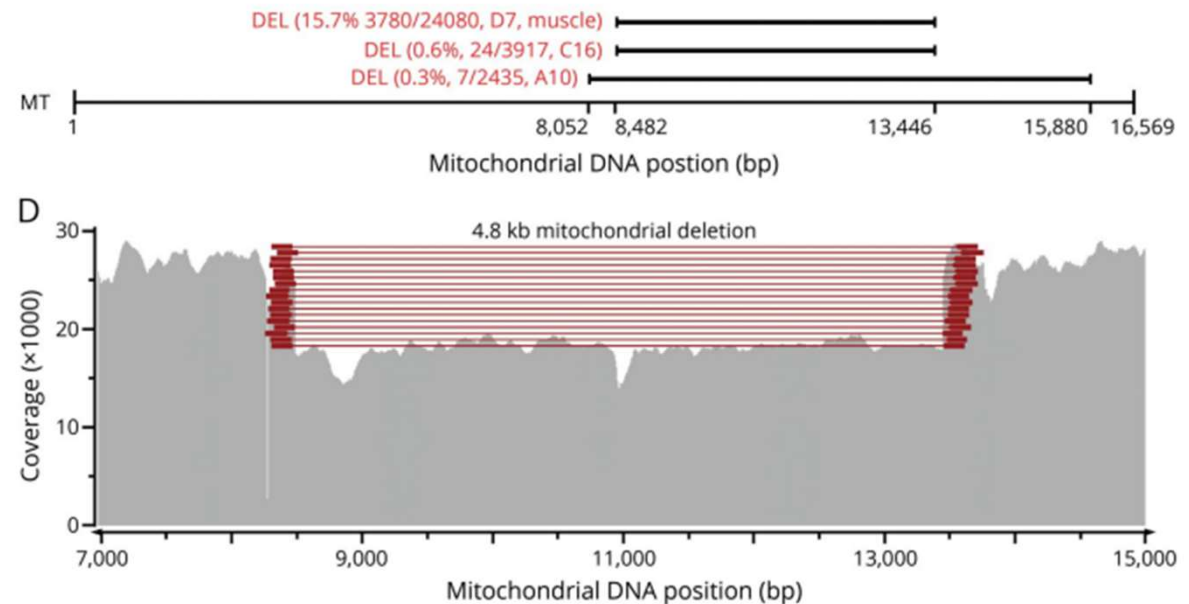
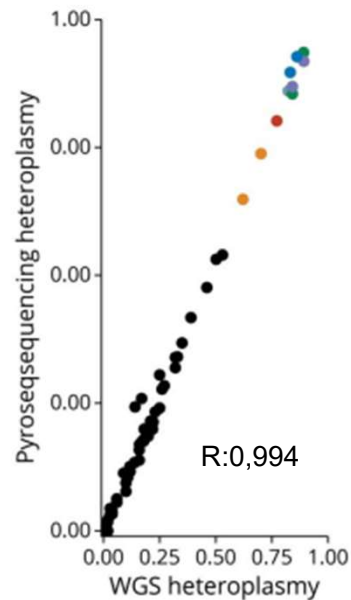


WGS: pipeline of the future/ presence



Clinical Trial > [BMJ. 2021 Nov 3;375:e066288. doi: 10.1136/bmj-2021-066288.](https://doi.org/10.1136/bmj-2021-066288)

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



mtDNA: variant interpretation



MITOMAP

MITOMAP
MITOMASTER
POLG Server
MitoScape

Tools

Help
 Search
 Index

Service provided by the
Center for Mitochondrial
& Epigenomic Medicine
at the Children's Hospital
of Philadelphia

You are here: Foswiki > MITOMAP Web > WebHome (05 Dec 2025, UnknownUser)

MITOMAP A human mitochondrial genome database

A compendium of polymorphisms and mutations in human mitochondrial DNA

MITOMAP reports published data on human mitochondrial DNA variation. If you would like to add a paper and its data into MITOMAP, please email a pdf to mitomap@chop.edu. We appreciate your help.

2025 Update #2: On **July 15, 2025** we added **673** new full-length (FL) and **786** new control region (CR) GenBank sequences to our database. This brings our total number of FL sequences to **62,556** and the number of CR sequences to **81,778**. Our SNVs now total **19,892**. We update our GenBank sequences every 4-6 months. Hand curation of variants and references continues weekly. See the [GenBank Frequency Info](#) page for details about our current sequence sets and update history.

★ We have starred our user Favorites for seeking information on specific variants and for understanding the contents of our database.

MITOMAP Quick Reference & Tools

★ **Allele Search** - get point mutation data based on position

★ **MITOMASTER** - analyze any human mito SNV or nucleotide sequence

★ **Tool Launchpad**

- The rCRS is GenBank number **NC_012920.1**. [Click here for details](#).

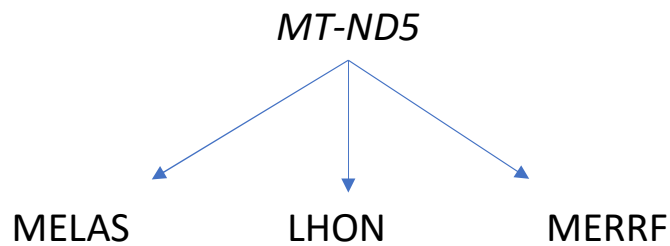


General References	Illustrations:
The Annotated Human Mitochondrial DNA Sequence	View Figures
The rCRS & other mtDNAs ★ GenBank Frequency Info	-Mitochondrial DNA Map
Amino Acid Translation Tables MitoTIP tRNA Scoring	-Eleven pathological mutations in tRNA
Mitochondrial References, ALL • A-L only • M-Z only	-Mitochondrial energetics
★ Haplogroup Markers ★ Most Common Variants	-Diabetes metabolism & the mitochondria
High Frequency Haplogroups Mitobank	-World migrations
mtDNA Polypeptide Assignments	-mtDNA Trees
mtDNA Function Locations (Gene Loci)	Simple mtDNA Tree: Europe, Asia, Africa
Archived Reports:	
Mitochondrial Human Genome Report	
Common Continent-Specific mtDNA Variants, c.1995	

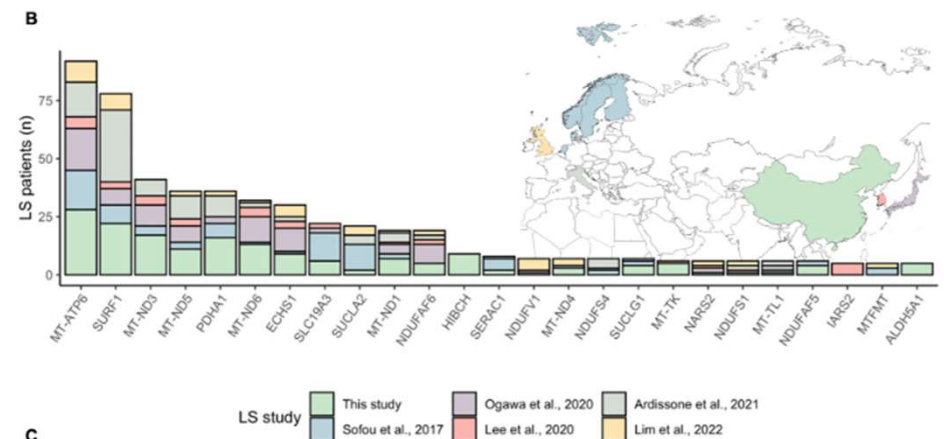
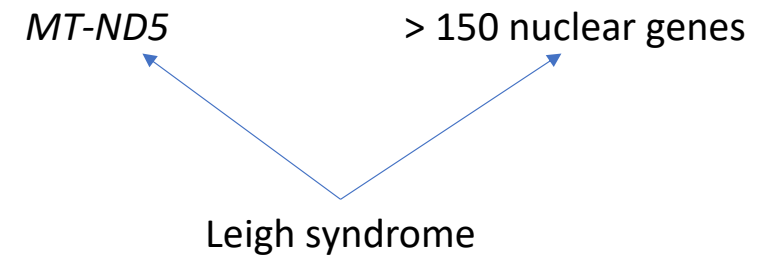
Mitochondrial diseases

- Two genomes, many genes AND

Allelic heterogeneity



Locus heterogeneity



Mitochondrial diseases



Mitochondrial diseases

- Prevalence: $>1/5000$ *
- Variable age of onset (neonatal – late adulthood)
- Often multisystemic
- Often progressive
- Poor treatment possibilities

* Ng and Turnbull, 2016



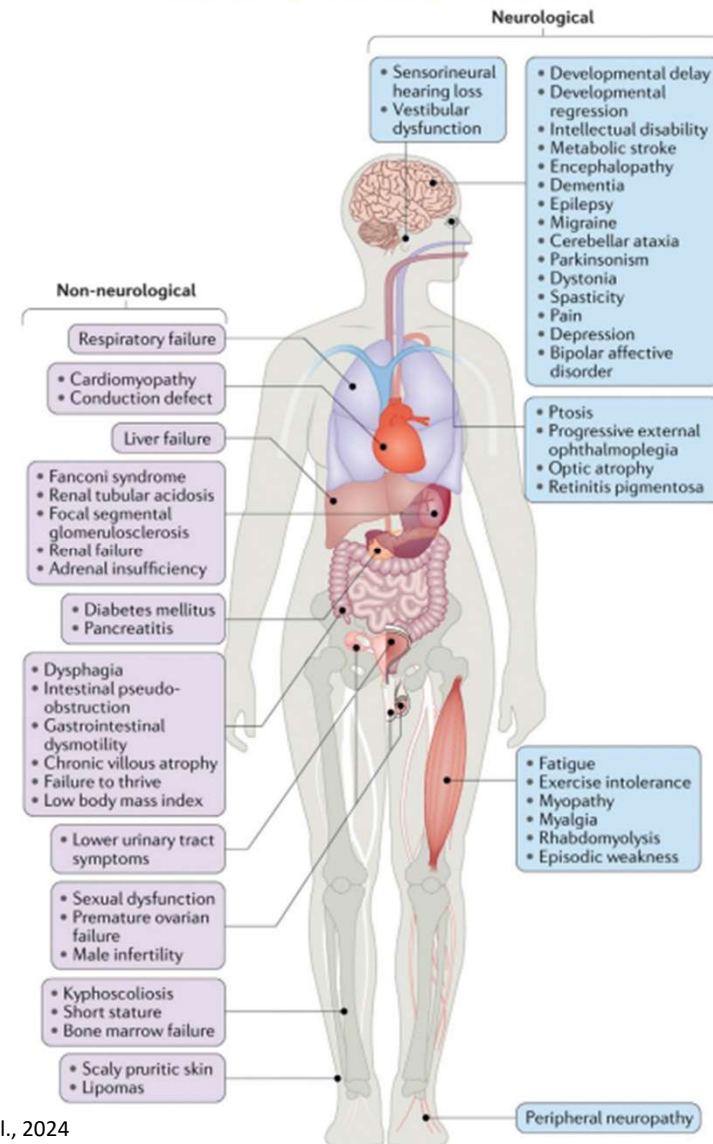
Clinical aspects

Prevalence:

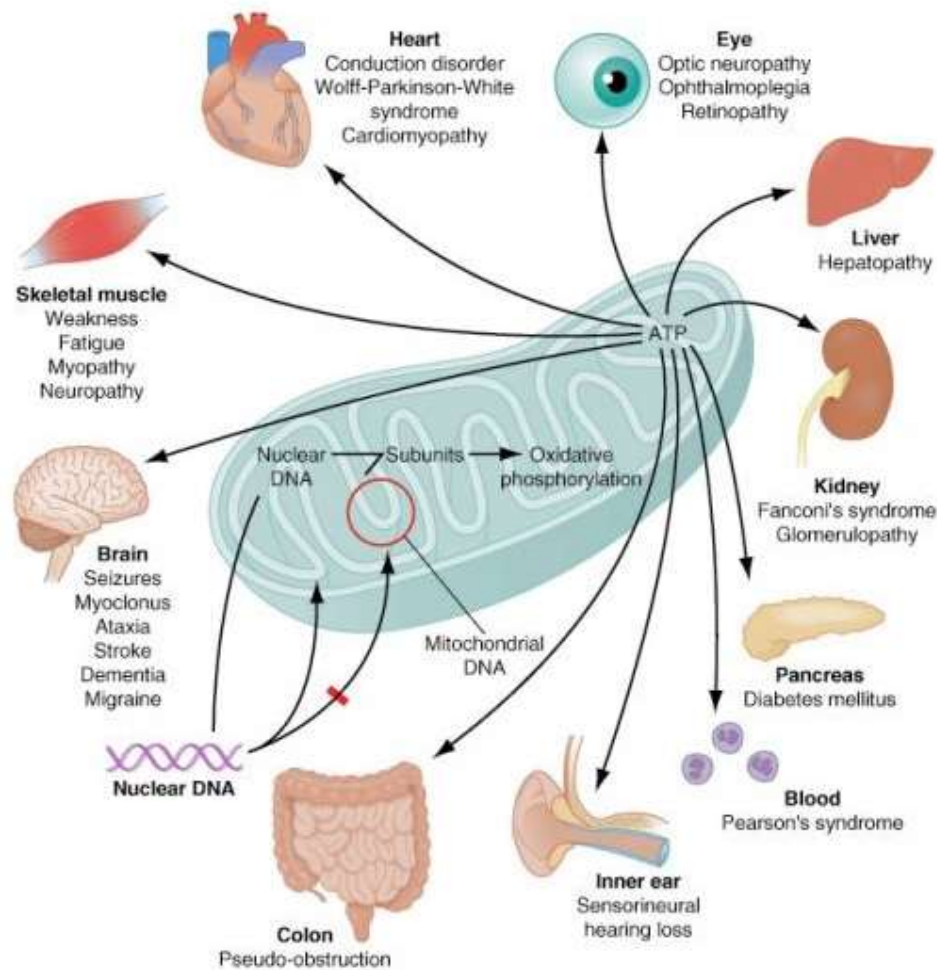
- 1/5000
- 5-15/100000 in children

Mito can affect any organ and cause any symptoms at any age.

PRIMARY MITOCHONDRIAL DISEASES



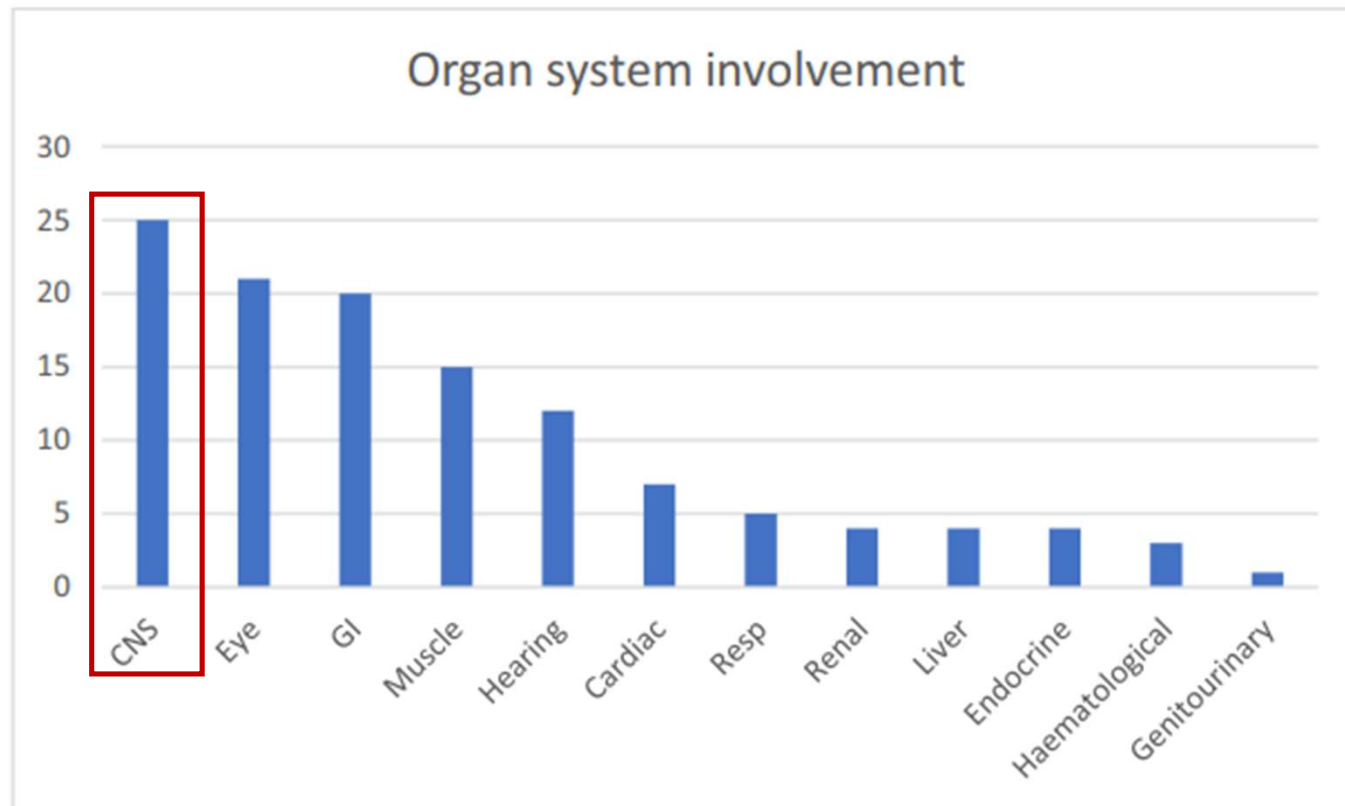
Clinical pictures



Fauci AS, Kasper DL, et al.: Harrison's Principles of Internal Medicine, 17th Edition

Involved organ systems in MD

Natural history of mitochondrial disorders: a systematic review





Mitochondrial disorders (MD) and the brain

- Group of MDs: most common cause of neurological disease in children



DD
ID
Hypotonia
Epilepsy (20-60%)
Movement disorders

Progressive



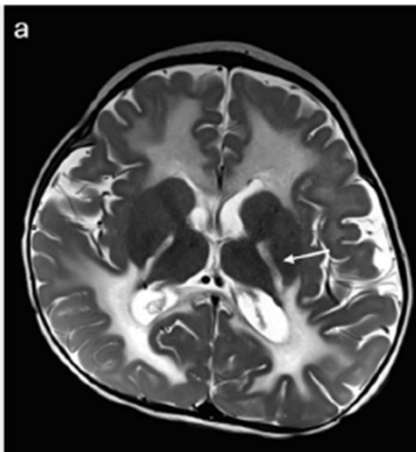
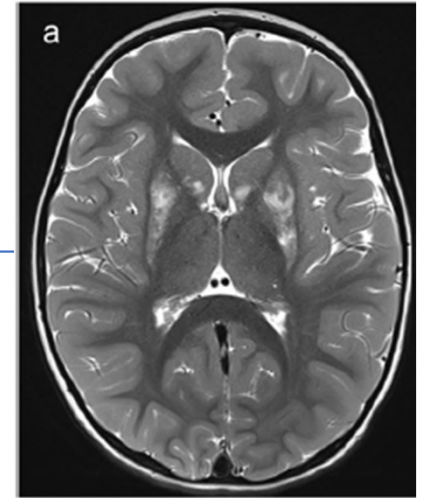
Mitochondrial Imaging Panel

1. Cortex	2. White Matter	3. Striatum	4. Cerebellum	5. Mito malformation
a	c	e	g	i
b	d	f	h	j
m.3243 A>G <i>POLG</i>	KSS <i>SURF1</i>	Leigh Leigh/MELAS	<i>MT-ATP6</i> <i>NUBPL</i>	PDH PDH

Brain MRI

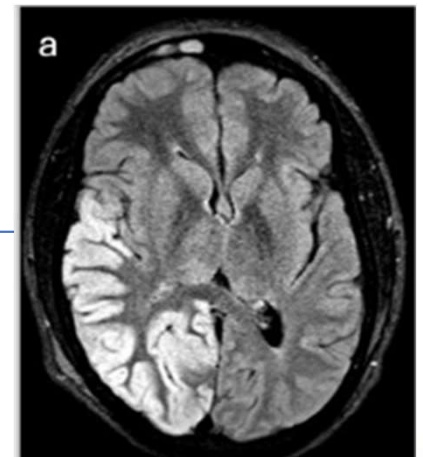


Both mtDNA and nDNA



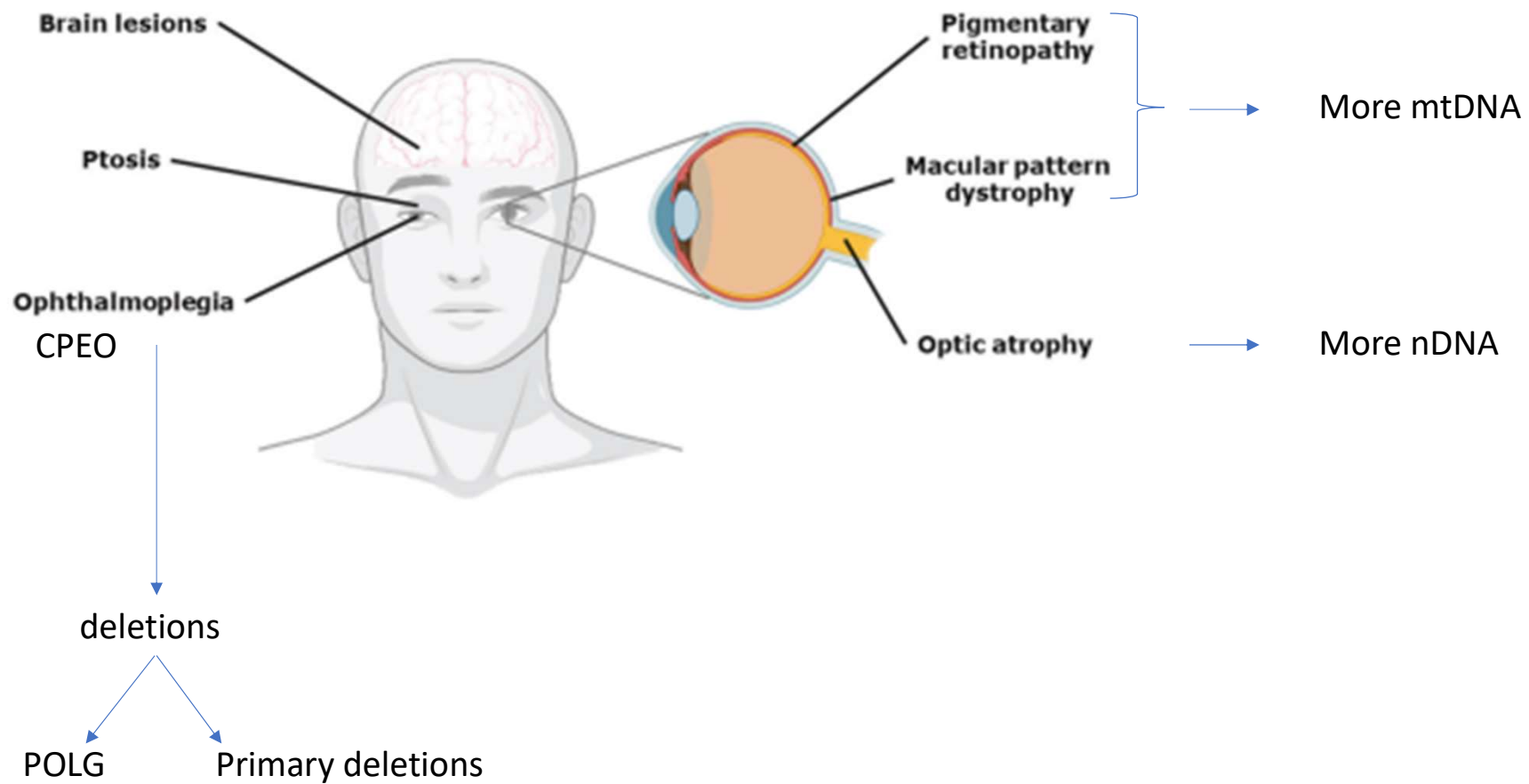
more likely
nDNA

more likely
mtDNA





Mitochondrial disorders: the eye



Mitochondrial diseases: LHON (Leber Hereditary Optic Neuropathy)

MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND4L, MT-ND5, MT-ND6, MT-CYB, MT-CO1, MT-CO3, MT-ATP6

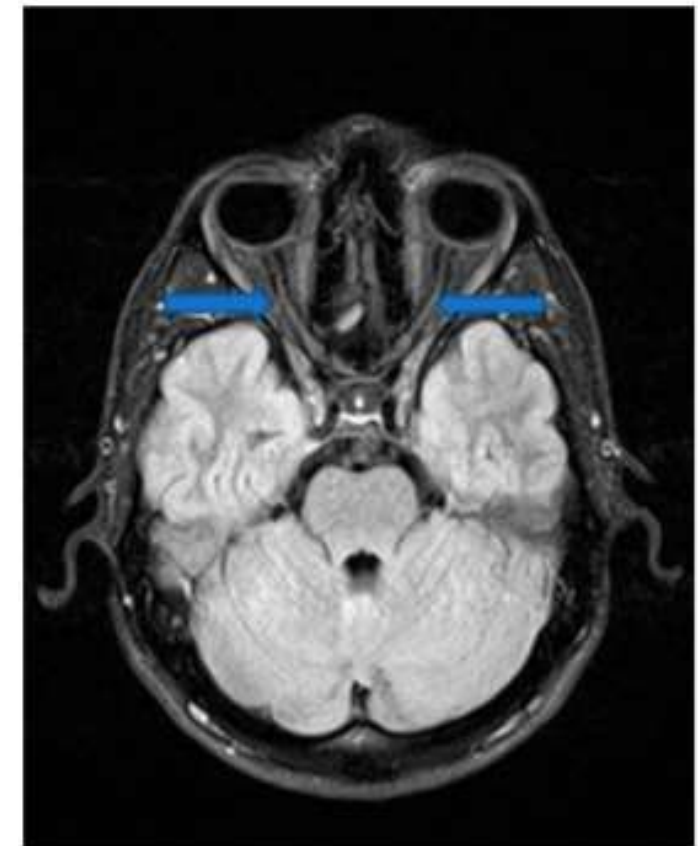
Clinical presentation

Subacute vision loss

Male predominance

Young onset (15-35y)

Increased risk by cigarette smoking



Therapy: Idebenone



mtDNA

Table 1 Mitochondrial DNA mutations associated with a kidney phenotype

	Mutation	Gene	Renal phenotype	References
Mitochondrial DNA point mutations				
	m.G586A	<i>mt-tRNA^{Phe}</i>	<u>TIN</u>	21
	m.A608G	<i>mt-tRNA^{Phe}</i>	TIN	20
	m.G3242A	<i>mt-tRNA^{Leu}</i>	Renal failure, RTA type 4	80,81
	m.3243	<i>mt-tRNA^{Leu}</i>	<u>FSGS</u>	12–14,23–26, 28,29,31–35,82
	m.3243	<i>mt-tRNA^{Leu}</i>	TIN	11,12
	m.A4269G	<i>mt-tRNA^{Ile}</i>	FSGS	17
	m.A5656G	*Noncoding	TIN	22
	m.A5728G	<i>mt-tRNA^{Ala}</i>	FSGS	18
	m.A5843G	<i>mt-tRNA^{Tyr}</i>	FSGS	19
	m.12425delA	<i>ND5</i>	Glomerulocystic disease, renal failure	36
Figure 1 label	Deletion size	Deletion location	Renal phenotype	References
Mitochondrial DNA deletions				
1	6,000 base pairs	–6,000–12,000	<u>Proximal tubulopathy</u>	45
2	7,500 base pairs	–6,100–13,600	FSGS, RTA	42
3	8,800 base pairs	–6,800–15,600	Distal tubulopathy	39
4	7,315 base pairs	7,325–14,639	Proximal tubulopathy, TIN	46
5	5,700 base pairs	–8,400–14,100	Proximal tubulopathy	43
6	4,977 base pairs	8,469–13,447	Proximal tubulopathy	44,47
7	2,800 base pairs	–10,000–12,800	Proximal tubulopathy, TIN	40
8	2,608 base pairs	10,598–13,206	TIN	41

Note: *Single noncoding base between *mt-tRNA^{Ala}* and *mt-tRNA^{Asn}*.

Abbreviations: DNA, deoxyribonucleic acid; *mt-tRNA*, mitochondrial transfer ribonucleic acid; TIN, tubulointerstitial nephritis; FSGS, focal segmental glomerulosclerosis; RTA, renal tubular acidosis; Phe, phenylalanine; Leu, leucine; Ile, isoleucine; Tyr, tyrosine; Ala, alanine; *ND5*, *NADH dehydrogenase 5*.

nDNA

Table 2 Nuclear genes encoding mitochondrial proteins associated with a kidney phenotype

Gene	Position	Renal phenotype	References
Coenzyme Q₁₀ biosynthesis			
<i>PDSS2</i>	Chromosome 6q21	<u>Nephrotic syndrome</u>	55
<i>COQ2</i>	Chromosome 4q21.23	Nephrotic syndrome	51–54
<i>COQ6</i>	Chromosome 14q24.3	Nephrotic syndrome	56
<i>COQ9</i>	Chromosome 16q21	Renal tubulopathy	50
Mitochondrial protein translation			
<i>SARS2</i>	Chromosome 19q13.2	Progressive renal failure, distal tubulopathy	60,61
<i>MRPS22</i>	Chromosome 3q23	Renal tubulopathy	63
<i>TSFM</i>	Chromosome 12q14.1	Renal tubulopathy	64
Posttranslational modification of mitochondrial proteins			
<i>XPNPEP3</i>	Chromosome 22q13.2	Interstitial fibrosis	65
Respiratory chain assembly and function			
<i>BCS1L</i>	Chromosome 2q35	Proximal tubulopathy, TIN	68
<i>SURF1</i>	Chromosome 9q34.2	RTA	69
<i>COX10</i>	Chromosome 17p12	Proximal tubulopathy	71
<i>TMEM70</i>	Chromosome 8q21.11	Proximal RTA	70
Mitochondrial DNA depletion			
<i>MPV17</i>	Chromosome 2p23.3	Renal failure	79
<i>C10orf2</i>	Chromosome 10q24.31	Proximal tubulopathy	72
<i>SUCLA2</i>	Chromosome 13q14.2	Methylmalonic aciduria	73,74
<i>SUCLG1</i>	Chromosome 2p11.2	Methylmalonic aciduria	75
<i>RRM2B</i>	Chromosome 8q22.3	Proximal tubulopathy	76,77
<i>DGUOK</i>	Chromosome 2p13.1	Cystathioninuria	78

Abbreviations: DNA, deoxyribonucleic acid; TIN, tubulointerstitial nephritis; RTA, renal tubular acidosis.

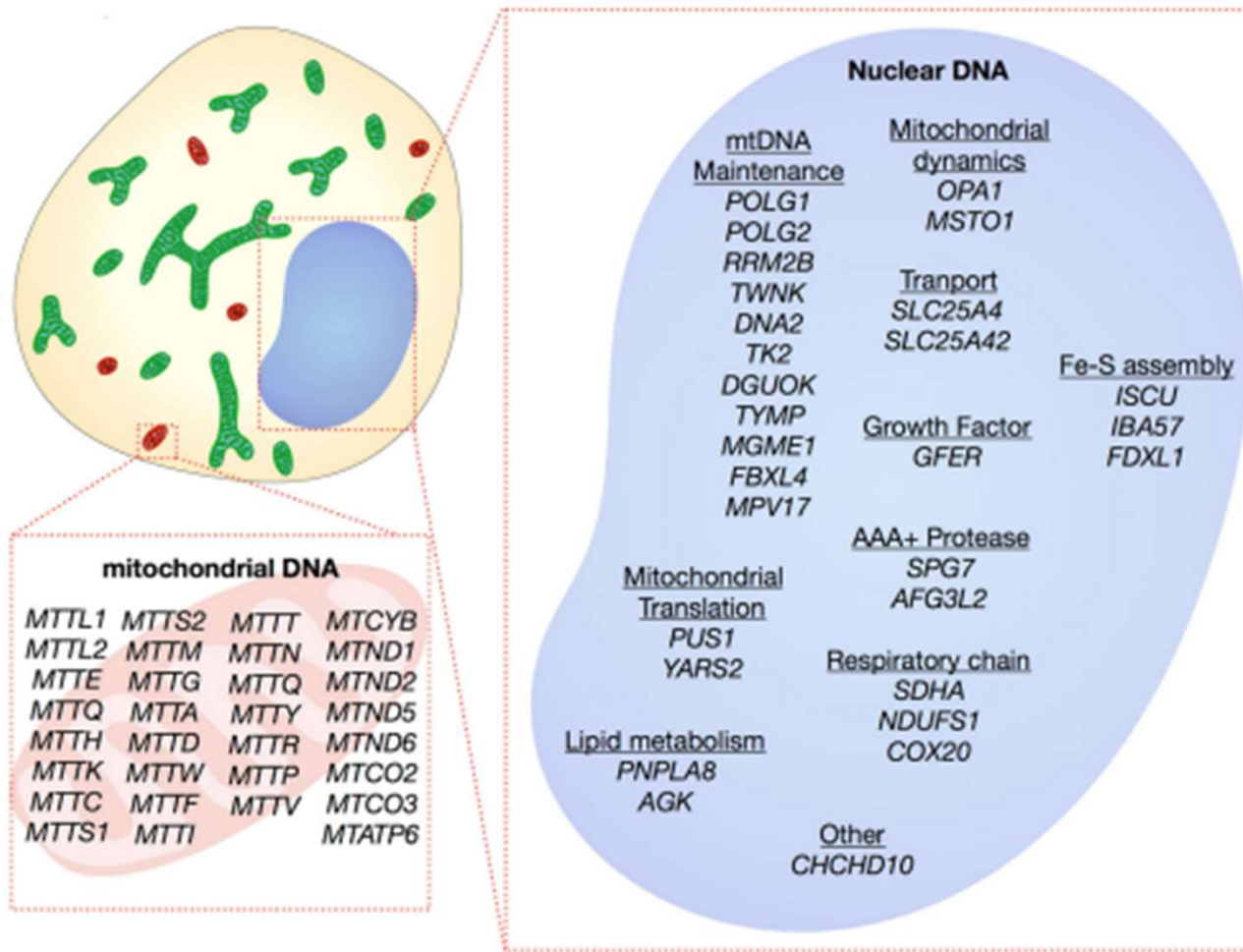


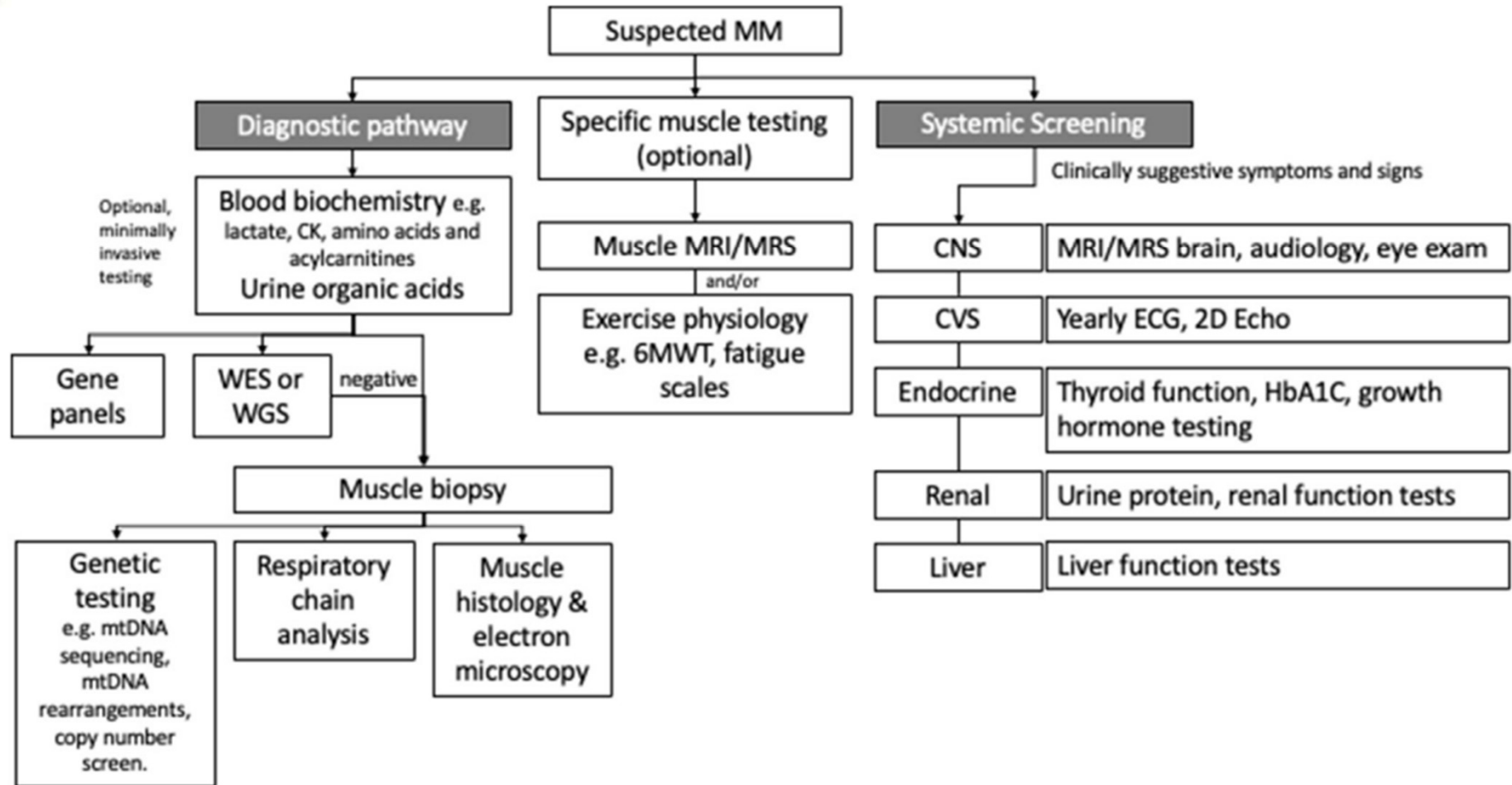
Mitochondrial disorders: muscle

- In children: isolated myopathy, as presenting symptom is uncommon
- myopathy more commonly one of the multisystem
- mitochondrial myopathies:
 - exercise intolerance
 - premature fatigue
 - muscle cramps
 - vomiting after exercise (cf. lactic acidosis)



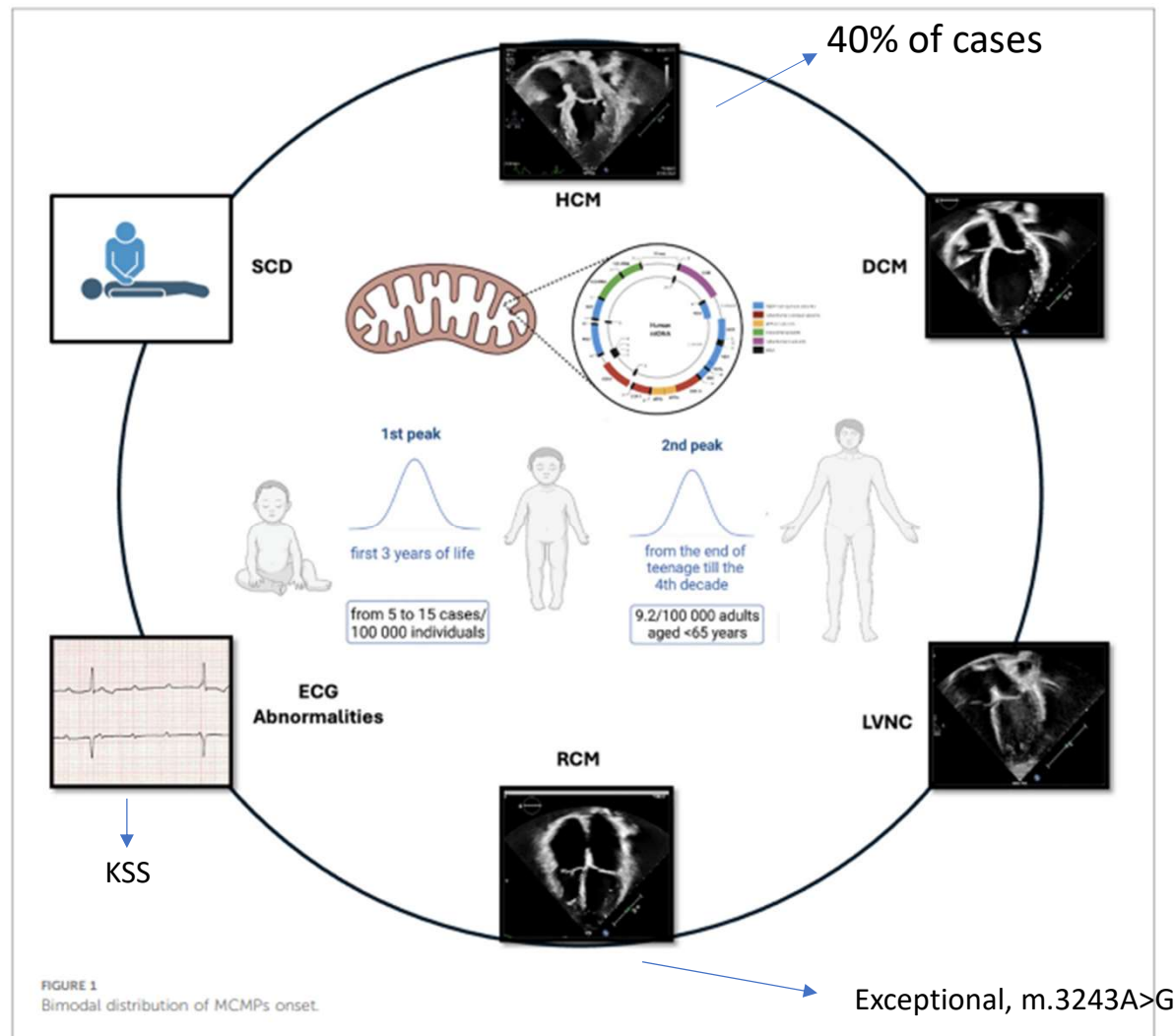
Mitochondrial disorders: muscle







Mitochondrial disorders: heart muscle





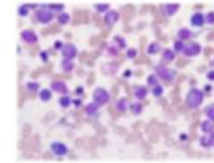
Mitochondrial disorders: heart muscle

- Barth syndrome
 - X-linked
 - TAZ
- Diagnostics
 - 3-Methylglutaconid-aciduria
- Treatment:
 - Elamipretide

Clinical presentation of Barth syndrome



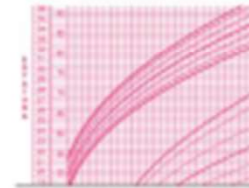
dilated
cardiomyopathy



neutropenia



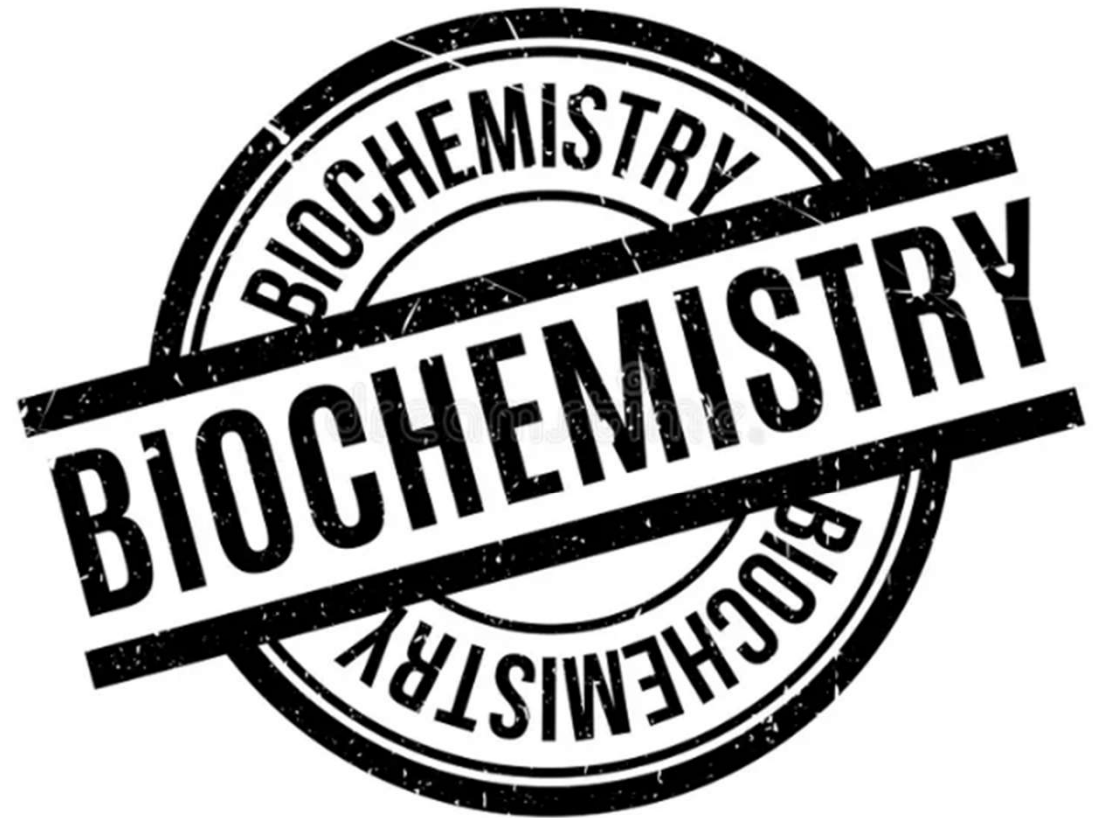
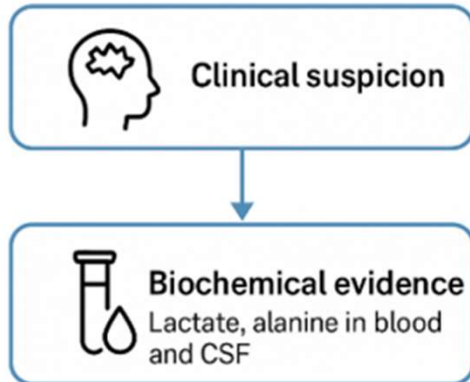
3-MGA-uria



growth failure

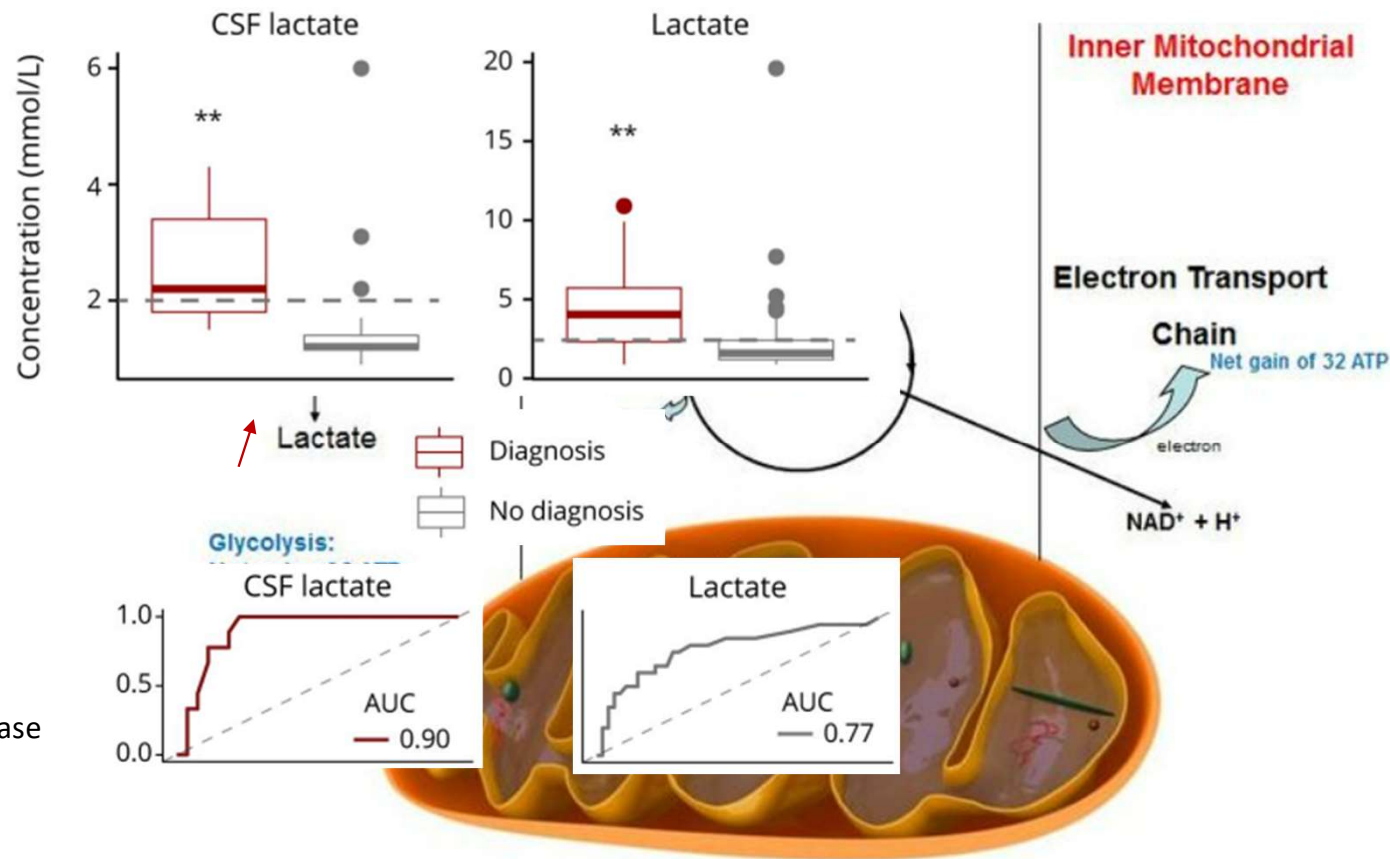


myopathy

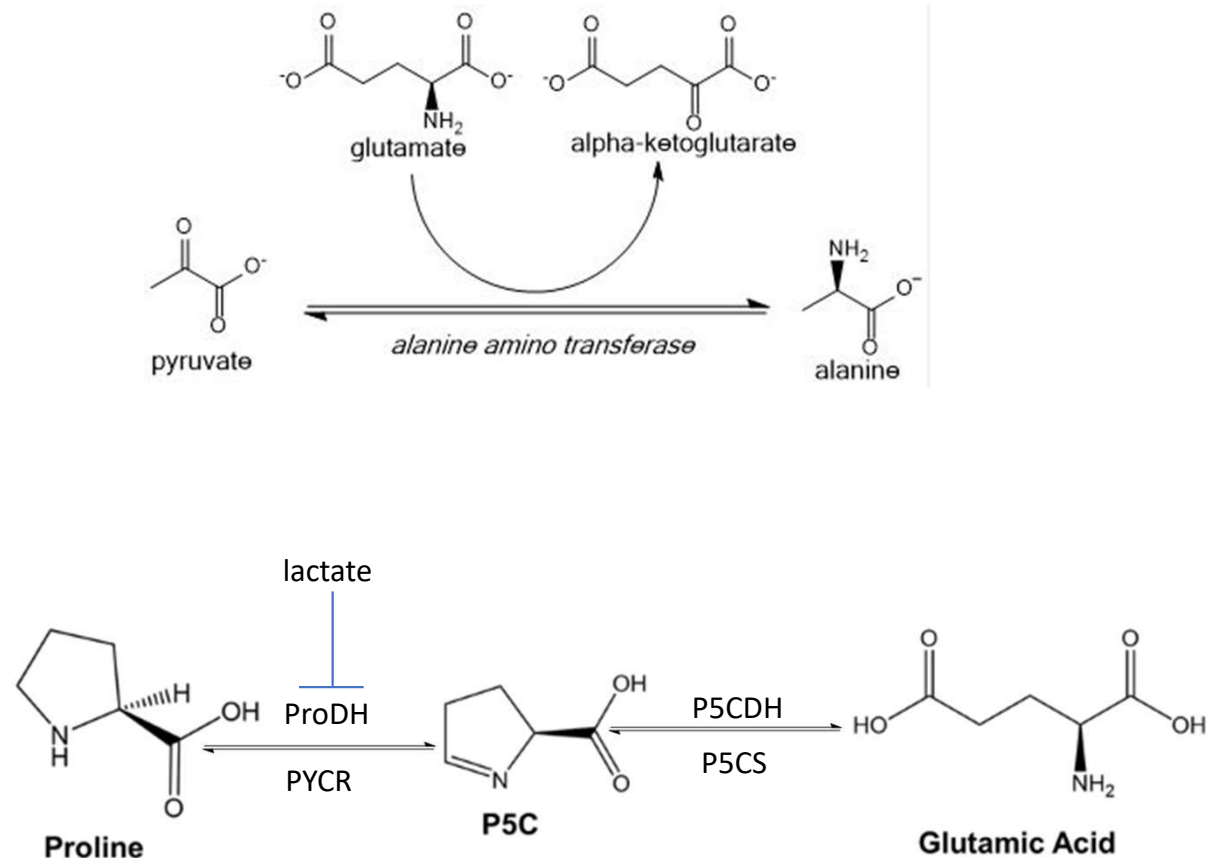
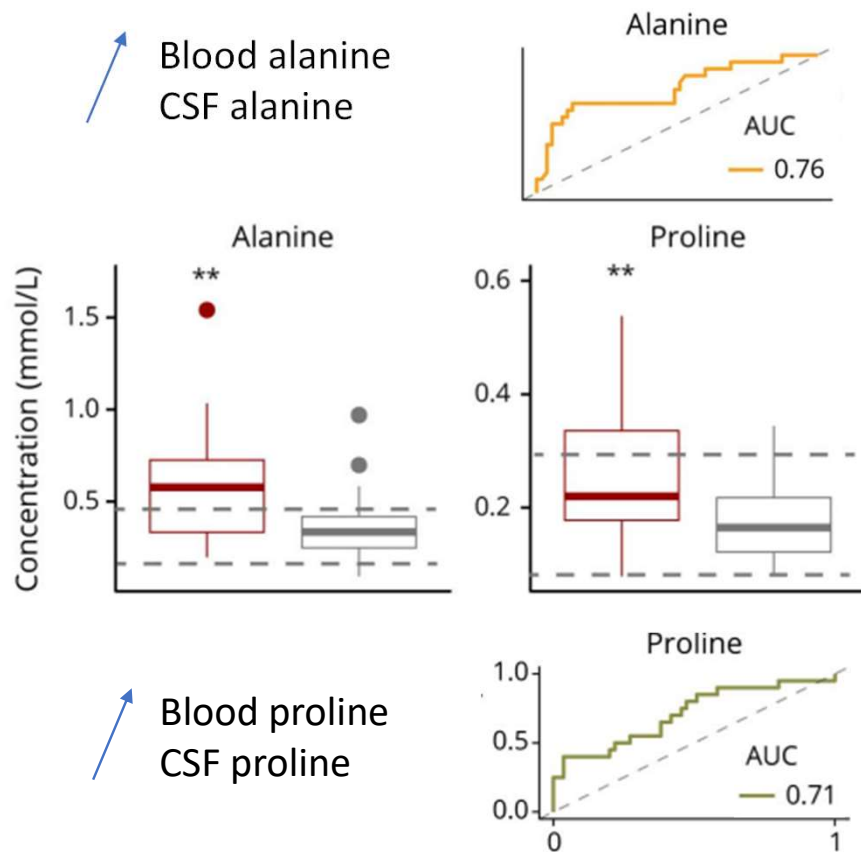


The quest for biomarkers: lactate - pyruvate

- Blood lactate: → postprandial
sens: 34 - 62%
spec: 83 - 100%
- CSF lactate:
more specific (CAVE status E)
- Urine lactate:
less correlation
- Pyruvate:
PDH and PC def
- L/P ratio: when elevated lactate
distinction between pyruvate and ETC disease



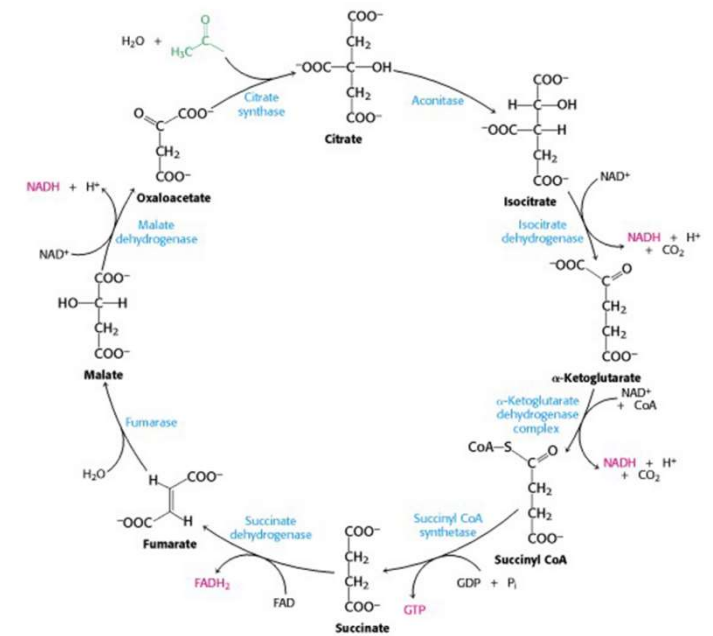
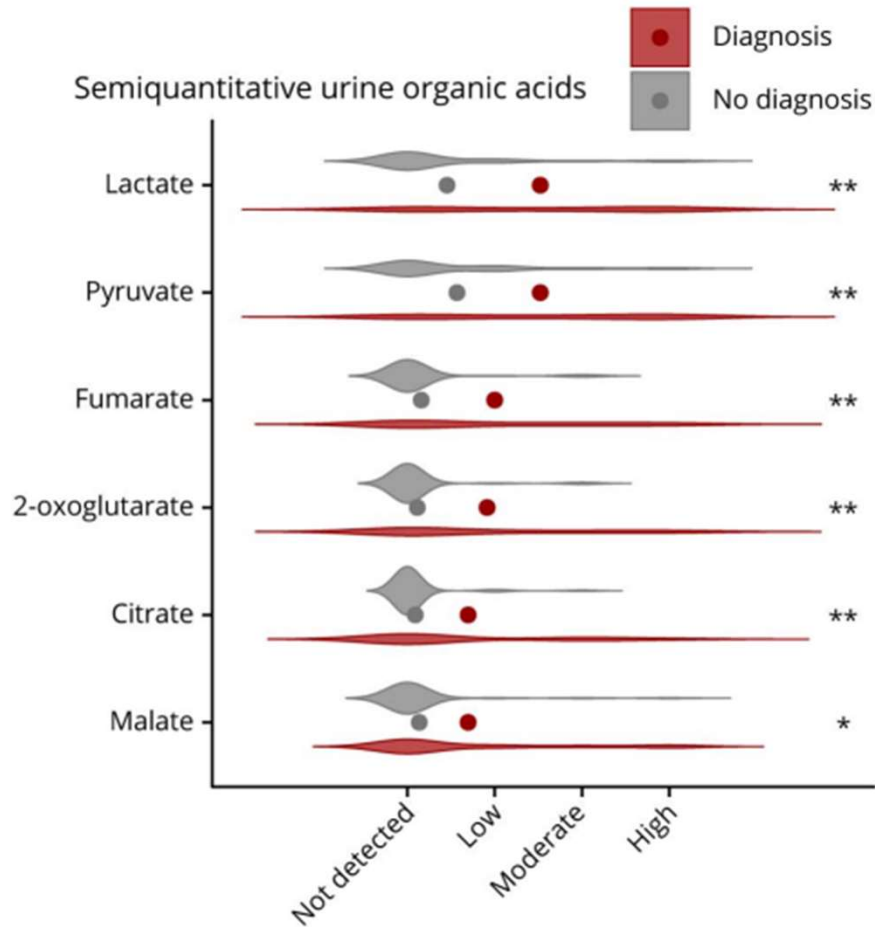
The quest for biomarkers: amino acids



Parikh et al., 2015; PMID: 25503498

Forni et al., 2021; PMID: 34056100

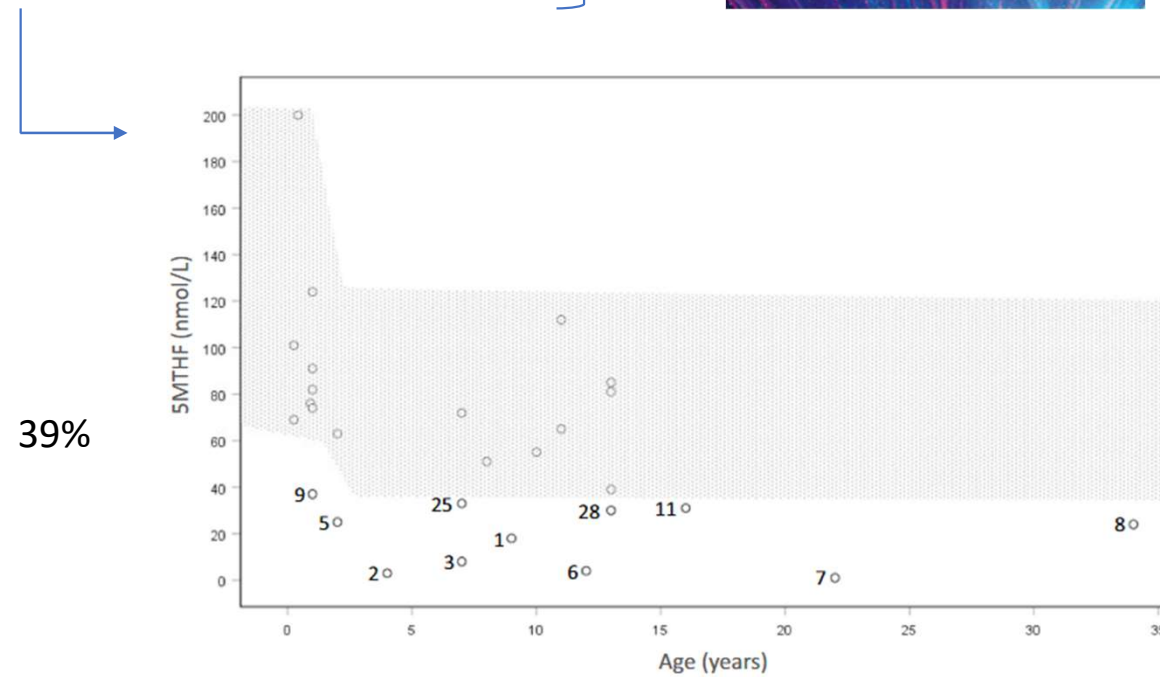
The quest for biomarkers: organic acids



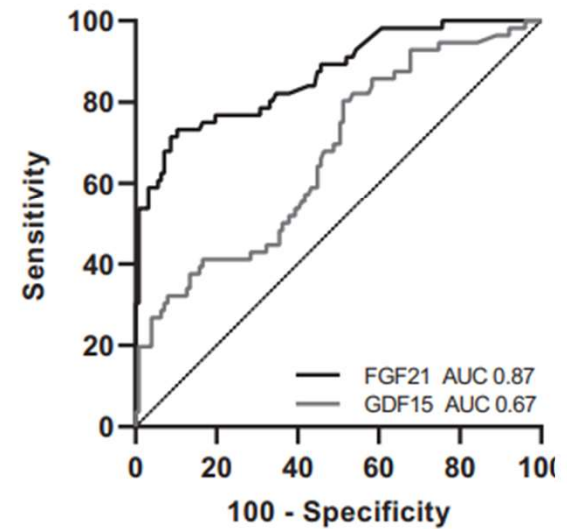
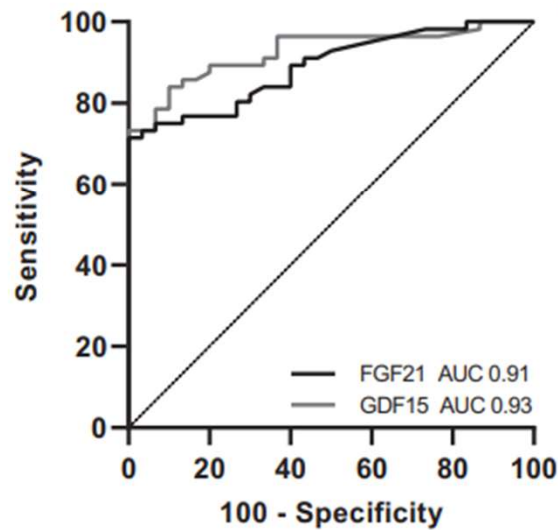
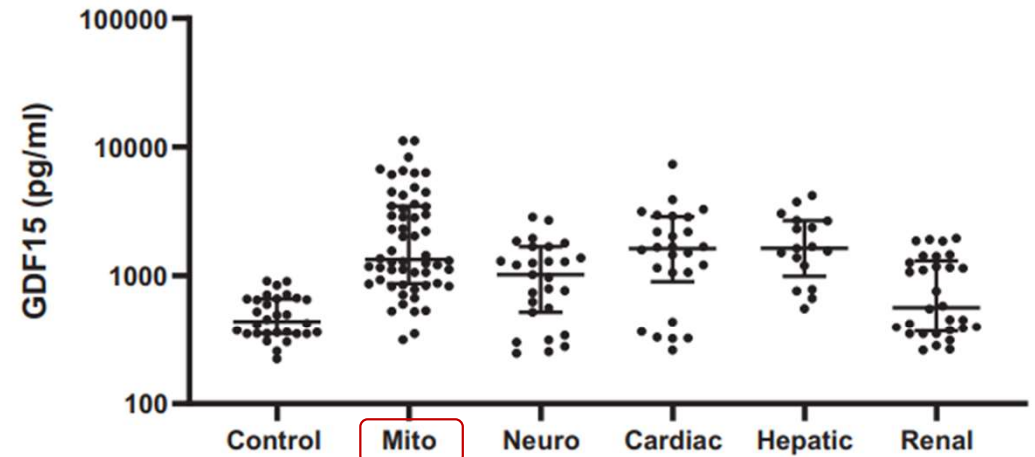
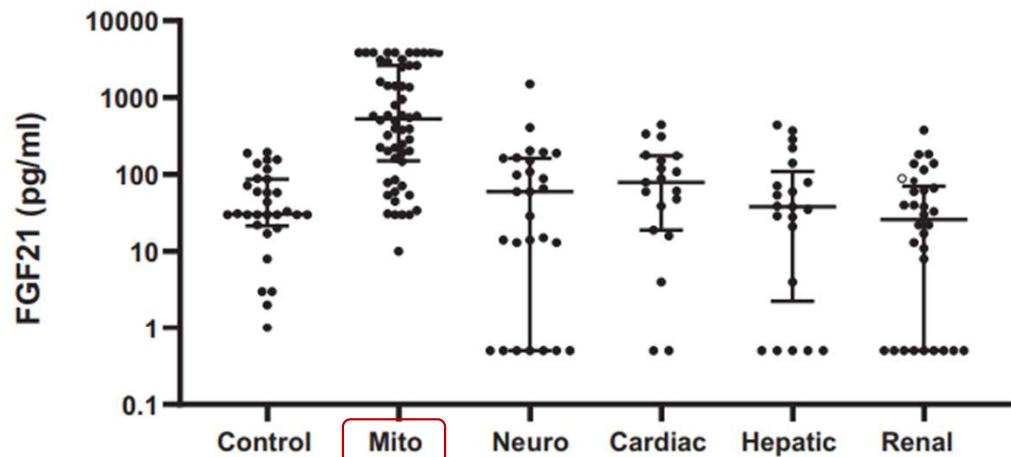
Parikh et al., 2015; PMID: 25503498

Forni et al., 2021; PMID: 34056100

- lactate
- amino acids
- 5-methyltetrahydrofolaat



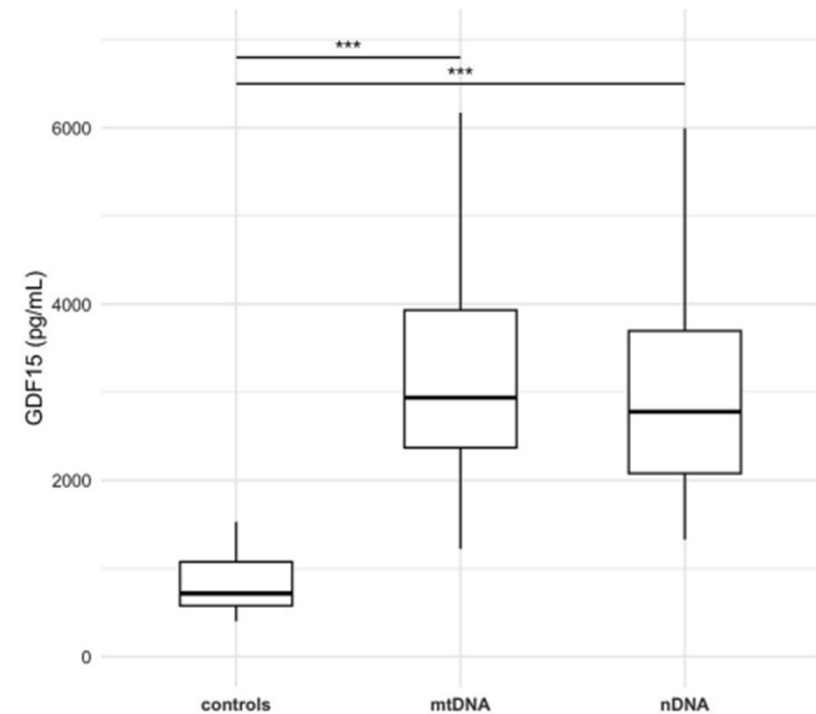
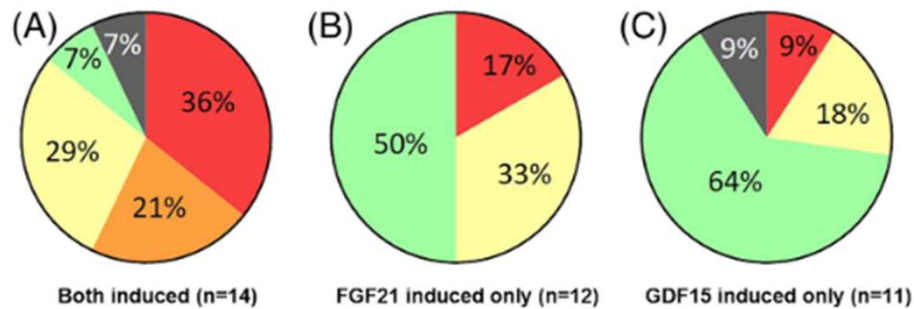
The quest for biomarkers: FGF21 and GDF15 in children



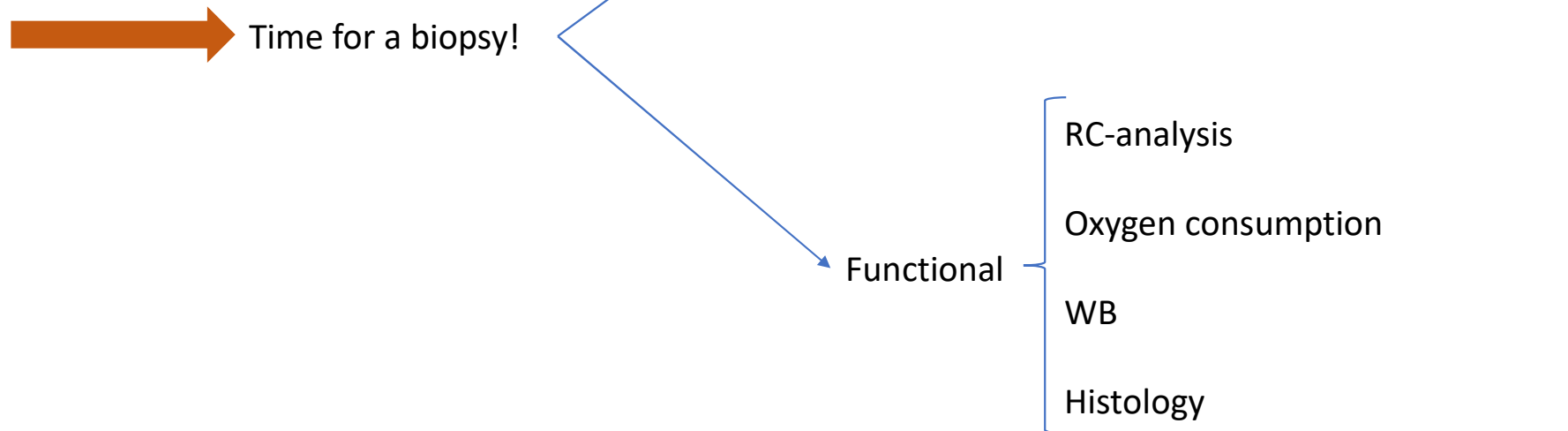
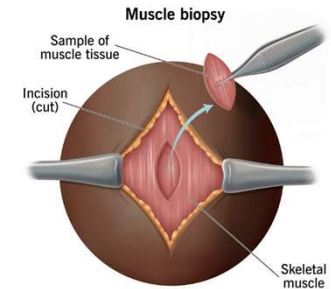
VS healthy controls

VS diseased controls

The quest for biomarkers: FGF21 and GDF15 in PMD

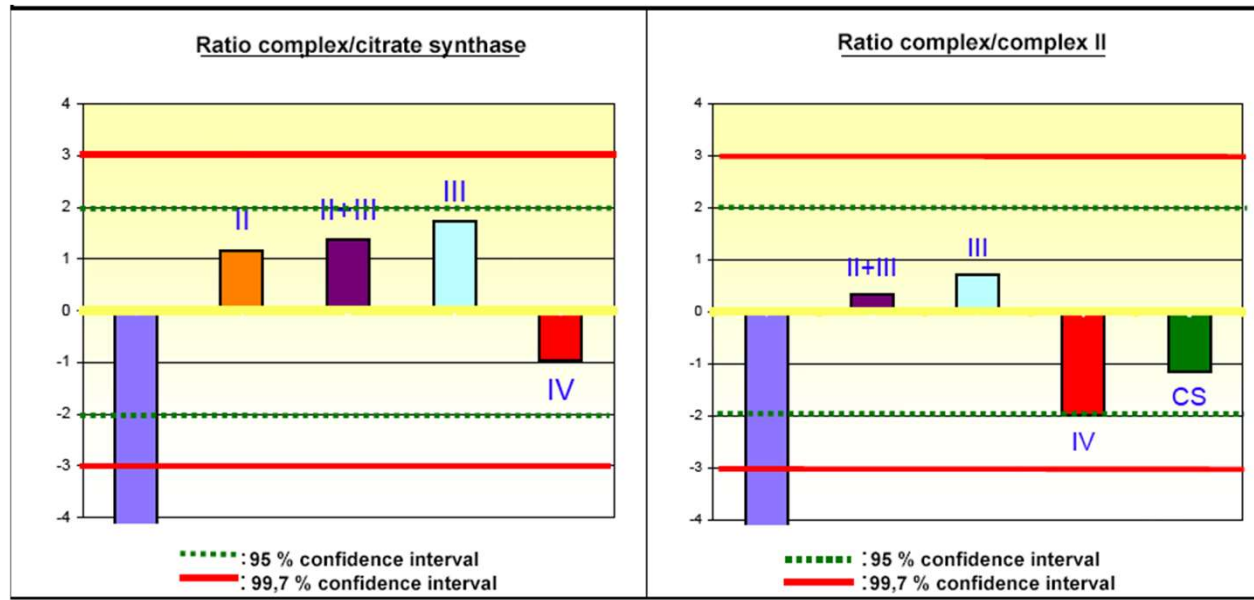


What in case of VUS or NUS?

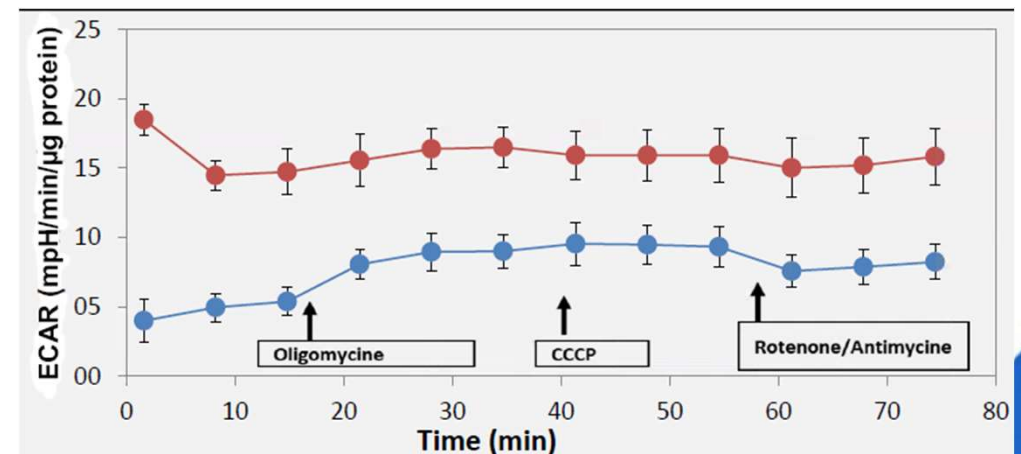
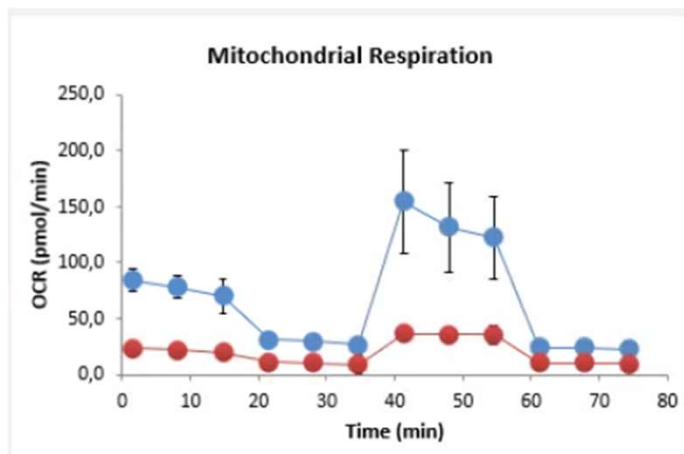


Functional analysis

RC-analysis

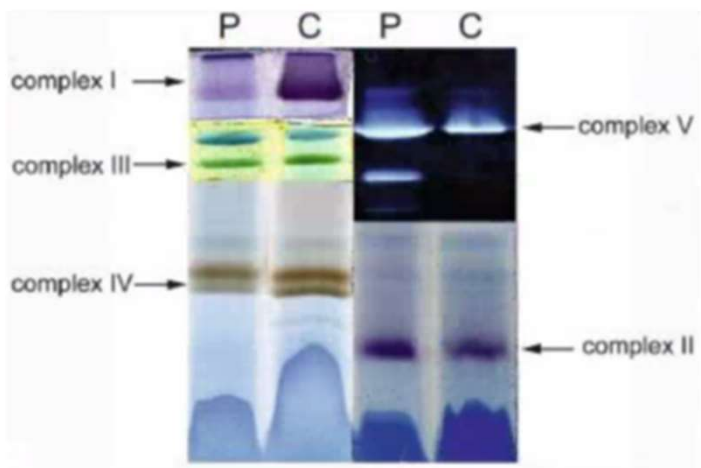


Oxygraph



Functional analysis

BN-PAGE
with IGA

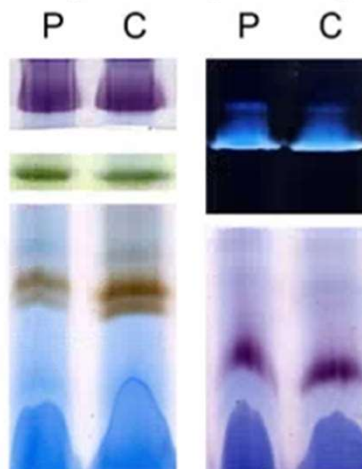


m.3243A>G

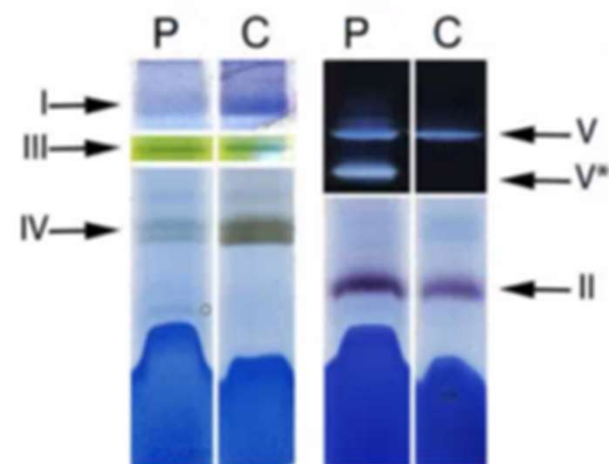
Complex

I
V
III
IV
II

In-gel activity staining

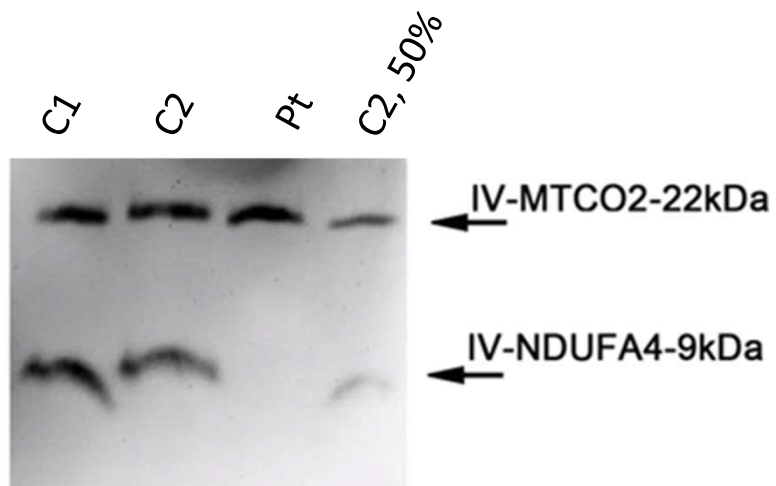


m.7402delC (*MTCO1*)



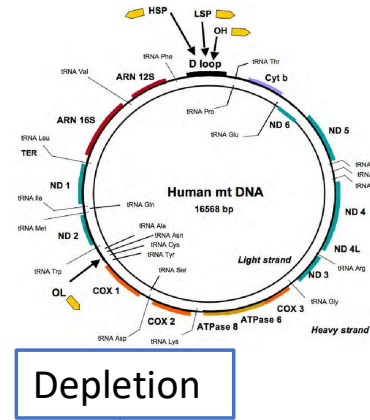
NARS2

WB



mtDNA alterations: biochemical consequences

KEEP IN MIND TISSUE SPECIFICITY



subunit

tRNA

rRNA

Isolated
complex
deficiency

Complex I	90%
-----------	-----

- Complex III
- Complex IV
- Complex V

Very rare

Deletions

combined complex deficiencies (except complex II)

Examples

mt-tRNA

MERRF

MELAS

mt-rRNA

Non-syndromic hearing loss

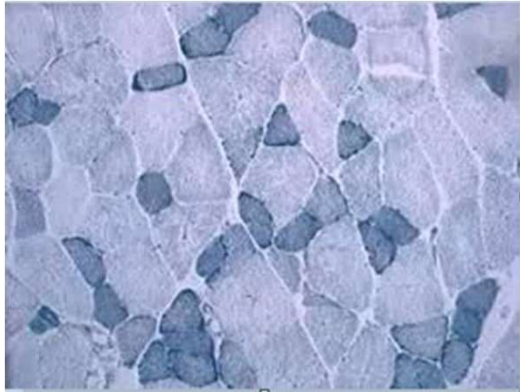
Deletion

- ▶ **Kearn-Sayre** **Pearson**

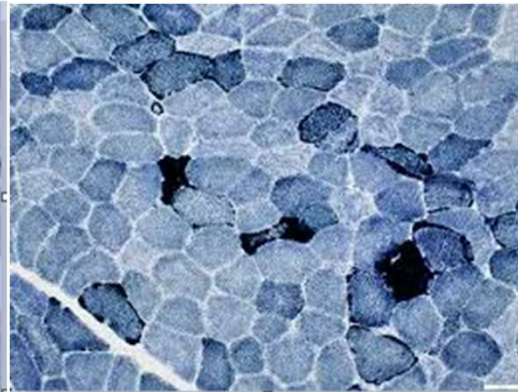
CPEO

Morphological analysis

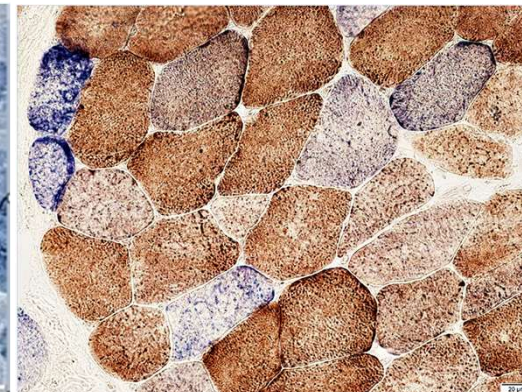
Pathology



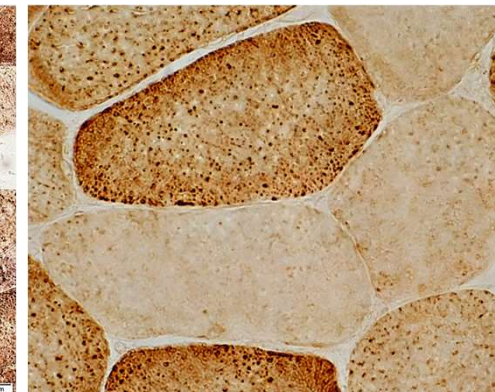
NADH



SDH
m.3243A>G

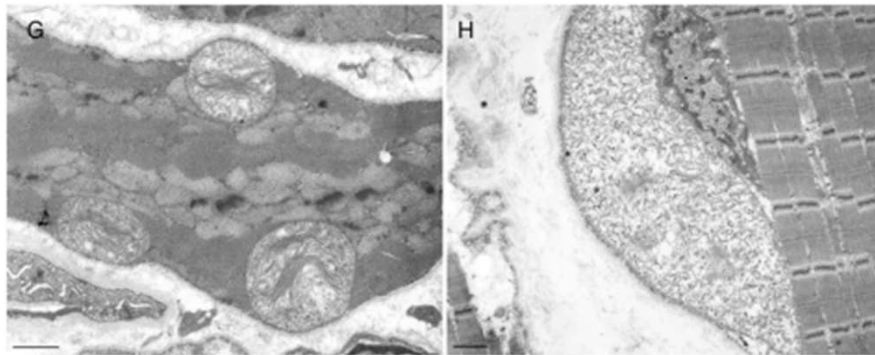


COX-SDH



COX

EM

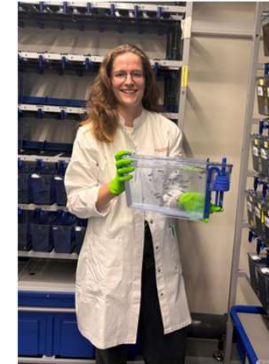
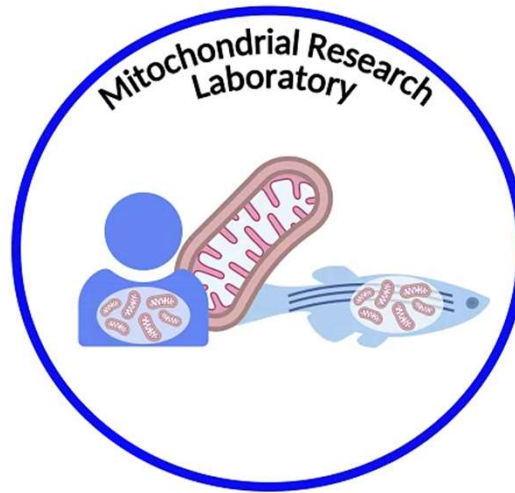
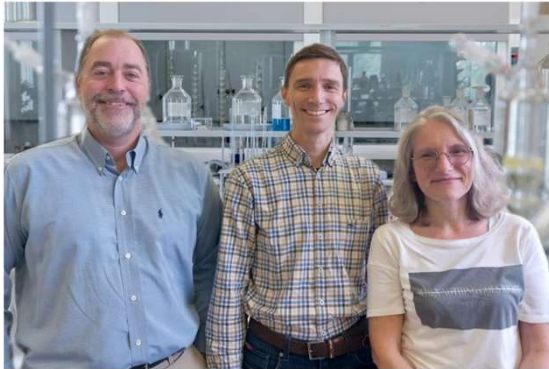


CHKB

EM to be preferred in children
as histology may be negative

Conclusions

- Always keep in mind a high suspicion for MD
- Screen for other organ involvement
- Check biochemical markers
- Perform genetic tests (nDNA – mtDNA)
 - Keep in mind tissue specificity!
- Perform advanced testing by tissue biopsy in case of VUS or no diagnosis



Joél Smet
Boel De Paepe
Lenie Van Hove
Arnaud Vanlander

ADDENDUM: 1

- Particular clinical pictures

Mitochondrial diseases: MELAS

M	mitochondrial myopathy
E	encephalopathy
L	lactic
A	acidosis
S	stroke like episodes

MT-TL1, *MT-TQ*, *MT-TH*, *MT-TC*, *MT-TS1*, *MT-TS2*, *MT-TK*, *MT-ND1*, *MT-ND5*, *MT-ND6*
m.3243A>G

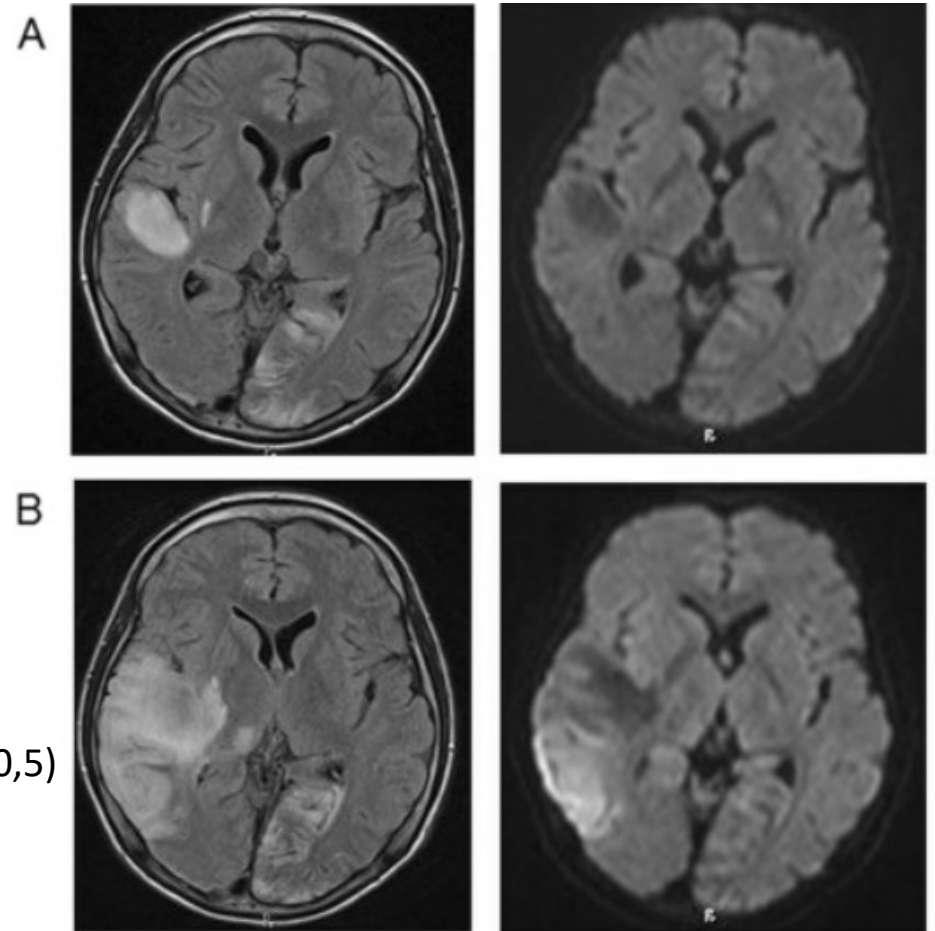
Clinical presentation

- teenage focal epilepsy
- progressive muscle weakness
- progressive cognitive decline
- cerebellar symptoms

m.3243A>G, *MT-TL1*,
22% blood
35% skin fibroblasts
37% saliva

Tissue specificity !

CSF lactate: 35,7mg/dl (ref: 13,7-20,5)



MELAS



Mitochondrial diseases: MERRF

MT-TK, MT-TL1, MT-TH, MT-TF, MT-TS1, MT-TS2, MT-TP
m.8344A>G

Clinical presentation

- Myoclonic epilepsy/generalized epilepsy
- progressive myopathy/exercise intolerance
- progressive cognitive decline
- cerebellar ataxia

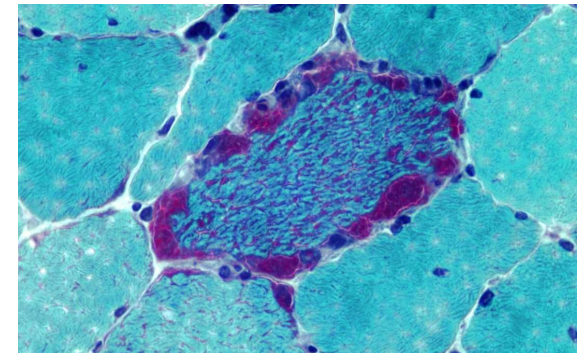
Additional clinical signs

- Ptosis – optic atrophy
- Peripheral neuropathy
- Sensorineural hearing loss
- Short stature

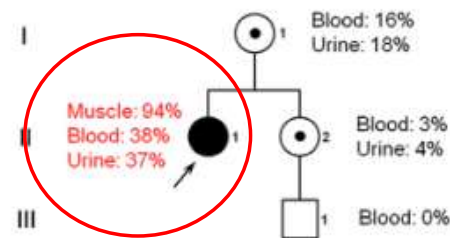
Less common clinical signs

- Cardiomyopathy
- Pigmentary retinopathy
- Ophthalmoparesis
- Multiple lipomas

M myoclonic
E epilepsy
R ragged
R red
F fibres



Ragged red fibres



Mitochondrial diseases: nonsyndromic deafness

M T - R N R 1

A

Clinical presentation

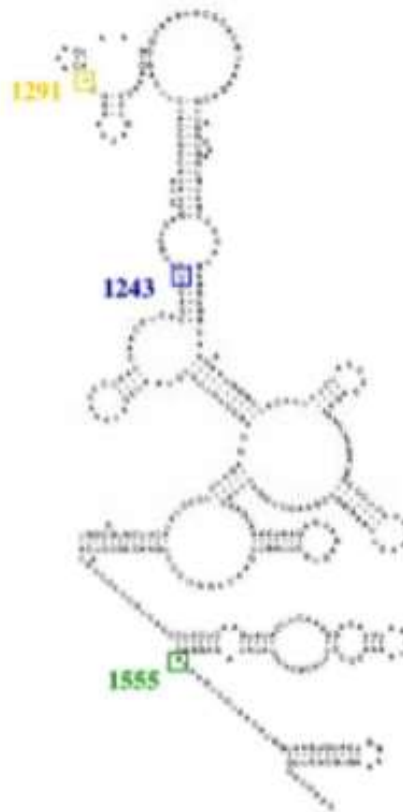
Deafness (isolated)

Sometimes caused by aminoglycoside treat

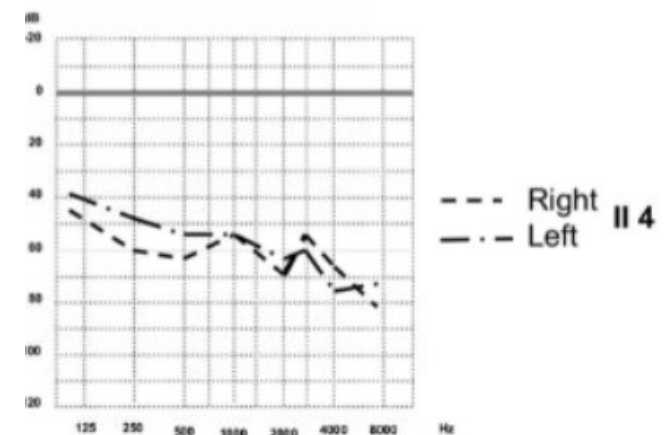
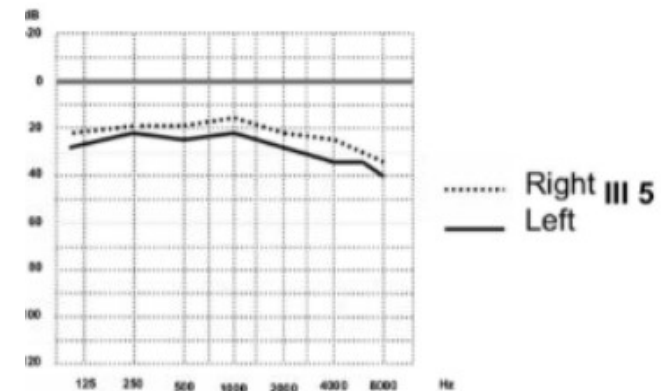
m.1555A>G

m.1243T>C *MT-RNR1*

m.1291T>C



Human mt 12S rRNA



Mitochondrial diseases: Leigh syndrome

MT-ND2, MT-ND3, MT-ND5, MT-ND6, MT-ATP6, MT-CO3, MT-TK

Many nuclear encoded genes

Clinical presentation

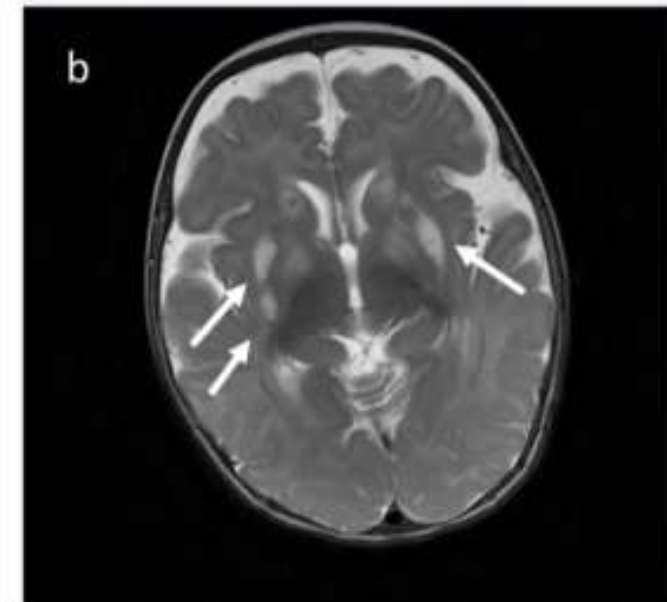
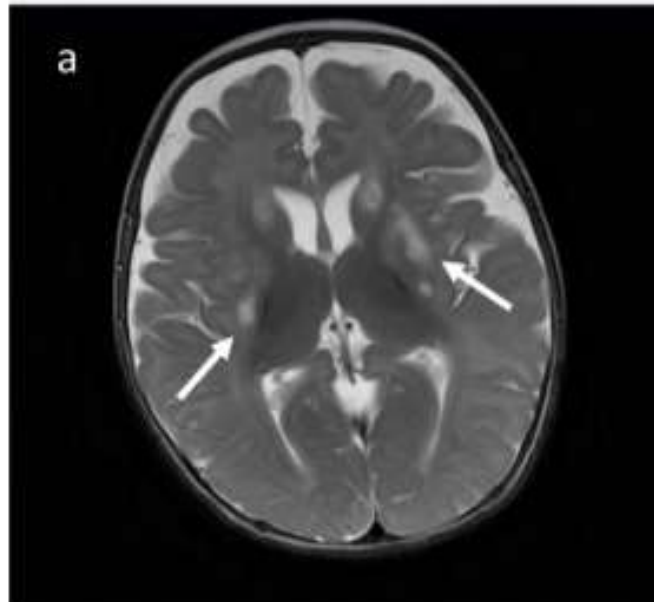
Typical symmetrical basal ganglia MRI lesions

1) Childhood presentation

- subacute necrotising encephalopathy
- developmental delay
- hypotonia
- epilepsy

2) Adult onset

- psychiatric features
- headache
- movement disorders



Mitochondrial diseases: deletions

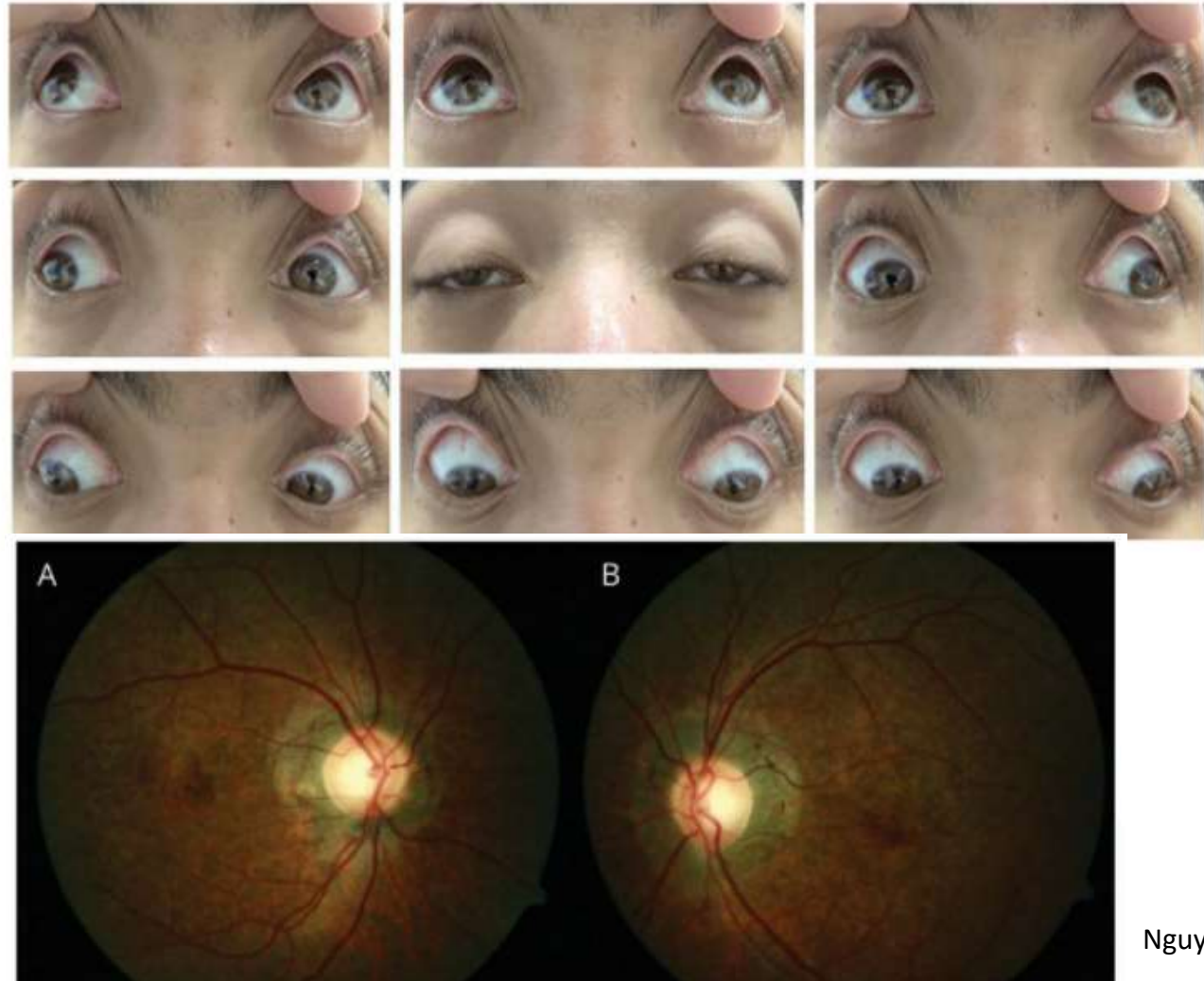
m t D N A d e l e t i o n

Kearns-Sayre syndrome

Clinical presentation

- teenage onset CPEO
- pigmentary retinopathy
- heart conduction problems
- ataxia
- deafness
- endocrine abnormalities

mtDNA deletion (1,0 -10 kb)



Mitochondrial diseases: deletions

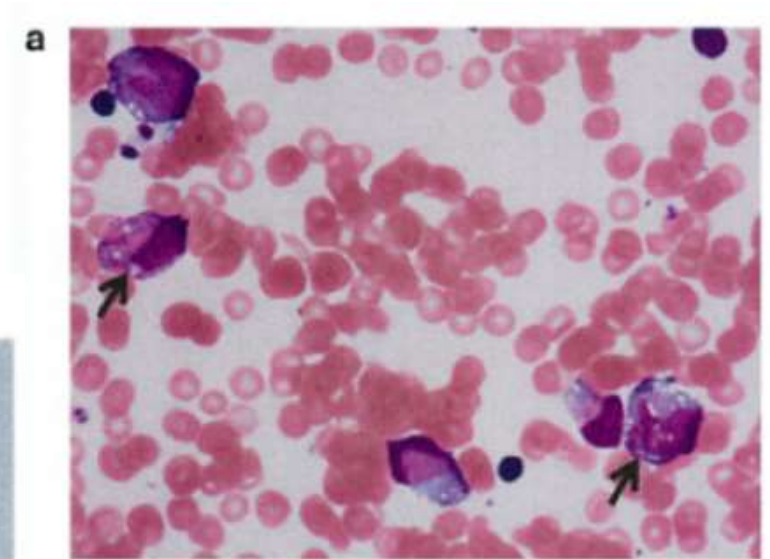
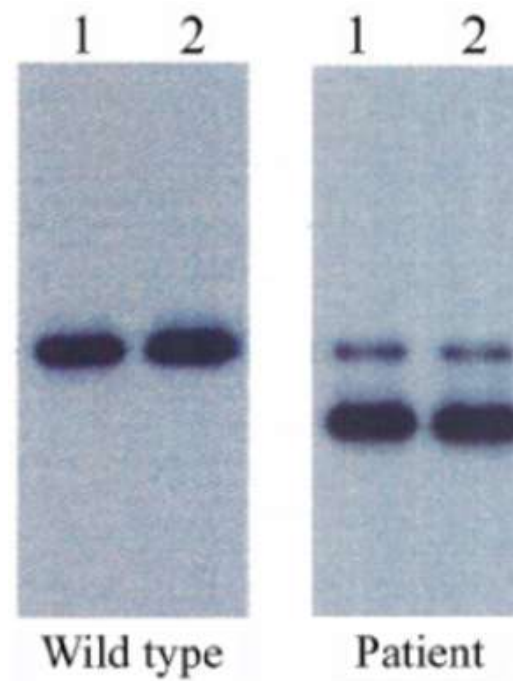
m t D N A d e l e t i o n

Pearson syndrome

Clinical presentation

- childhood onset → early dismiss (<3y)
- bone marrow dysfunction
- exocrine pancreas dysfunction
- → sometimes evolving towards Kearns sayre

mtDNA deletion

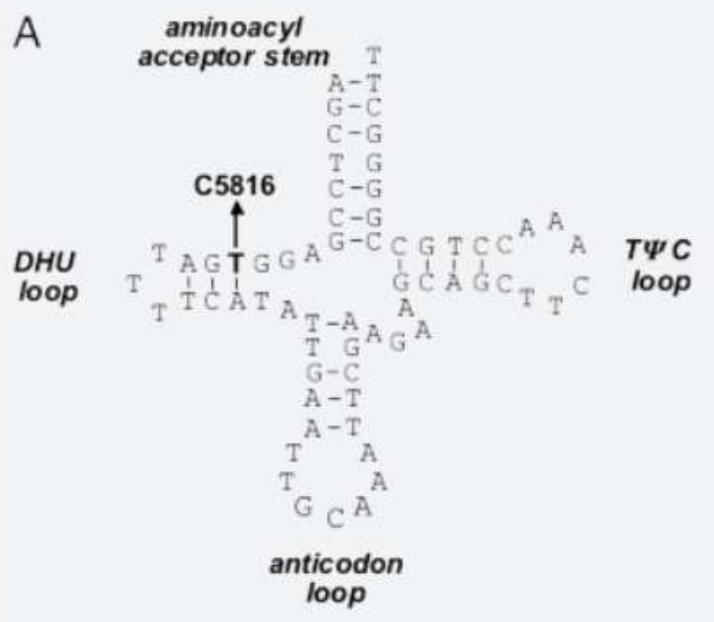
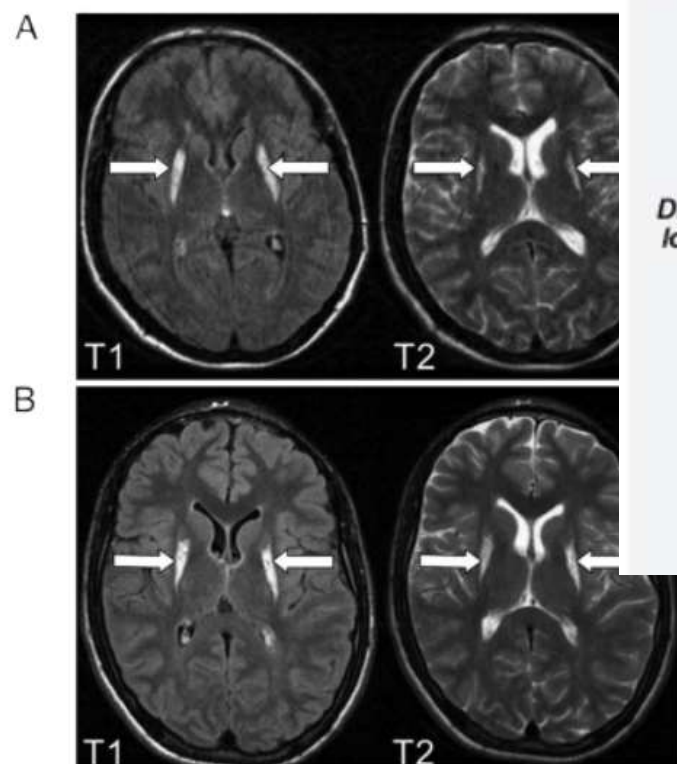


Mitochondrial diseases: tRNA

MT-TC

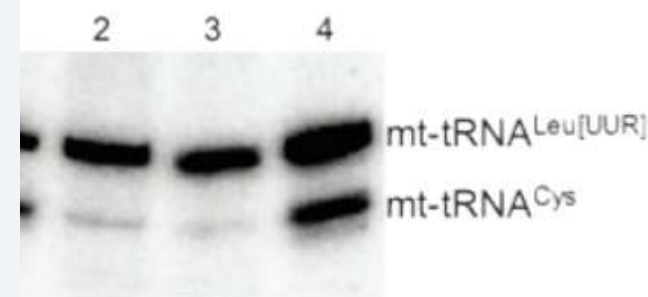
Clinical presentation

Figure 1 Symmetrical basal ganglia necrosis in Family 1



s with

psy



m.5816A>G, *MT-TC*,
100% muscle and blood

Homoplasmy

AV1 (B) Histochemical section of skeletal muscle from Patient 3, dual stained for cytochrome c oxidase (COX) and succinate dehydrogenase (SDH) activities, revealing approximately 15% COX-deficient fibers.

Arnaud Vanlander; 24/11/2021

Mitochondrial diseases: tRNA

M T - T D

Clinical presentation

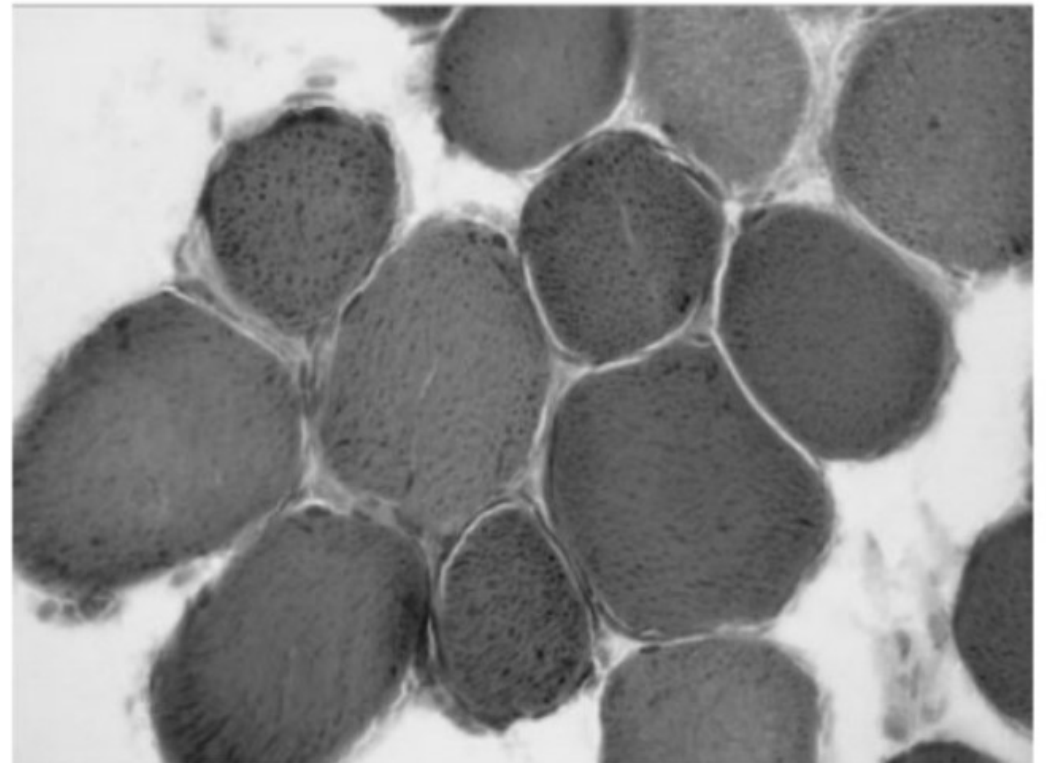
childhood onset
exercise intolerance
progressive

m.7526 A>G, *MT-TD*
100% skeletal muscle

3% blood and skin fibroblasts!

Tissue specificity !

Maternal testing: undetectable mutation



Mitochondrial diseases: tRNA

M T - T F

Clinical presentation

Adult onset exercise intolerance, progressive

Hearing loss

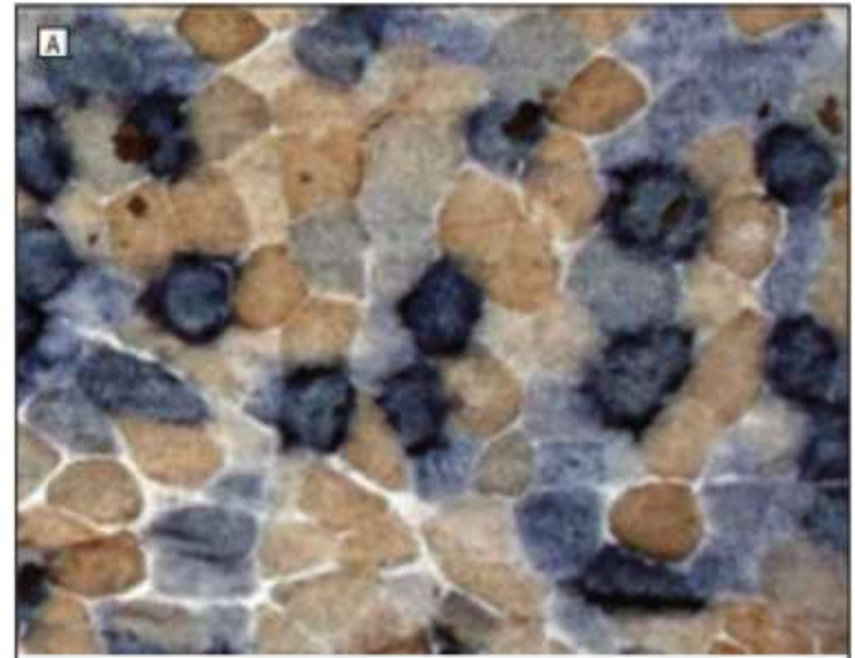
Variable age of onset!

m.622 G>A, *MT-TF*

88% skeletal muscle

66% blood

36% urine

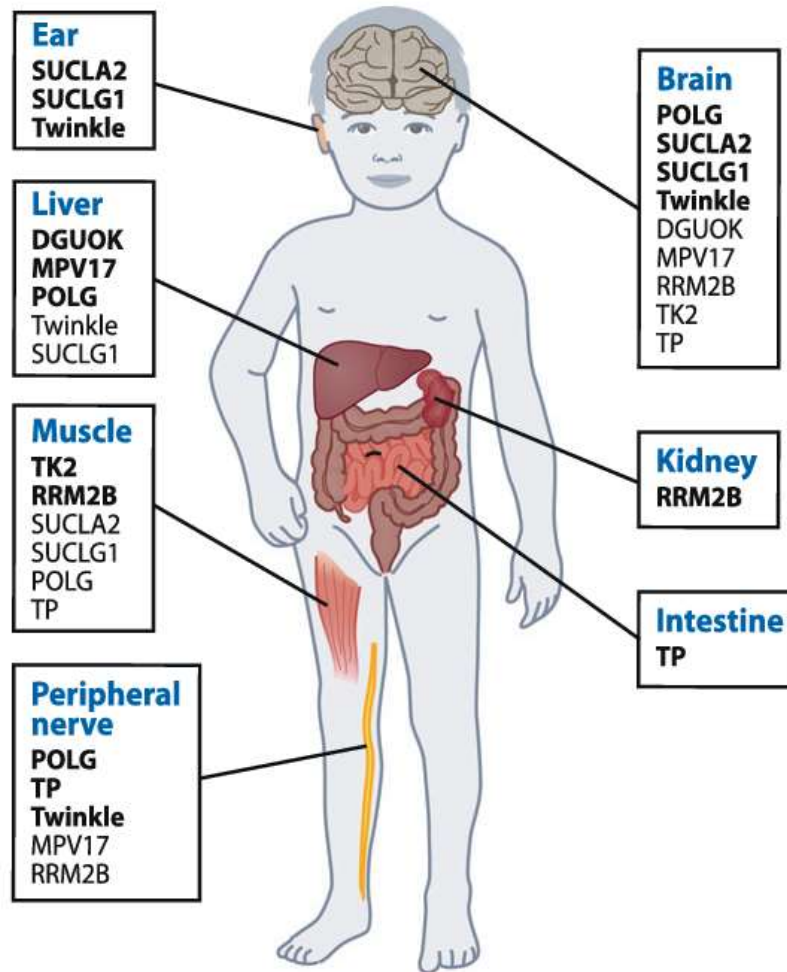


Mitochondrial diseases

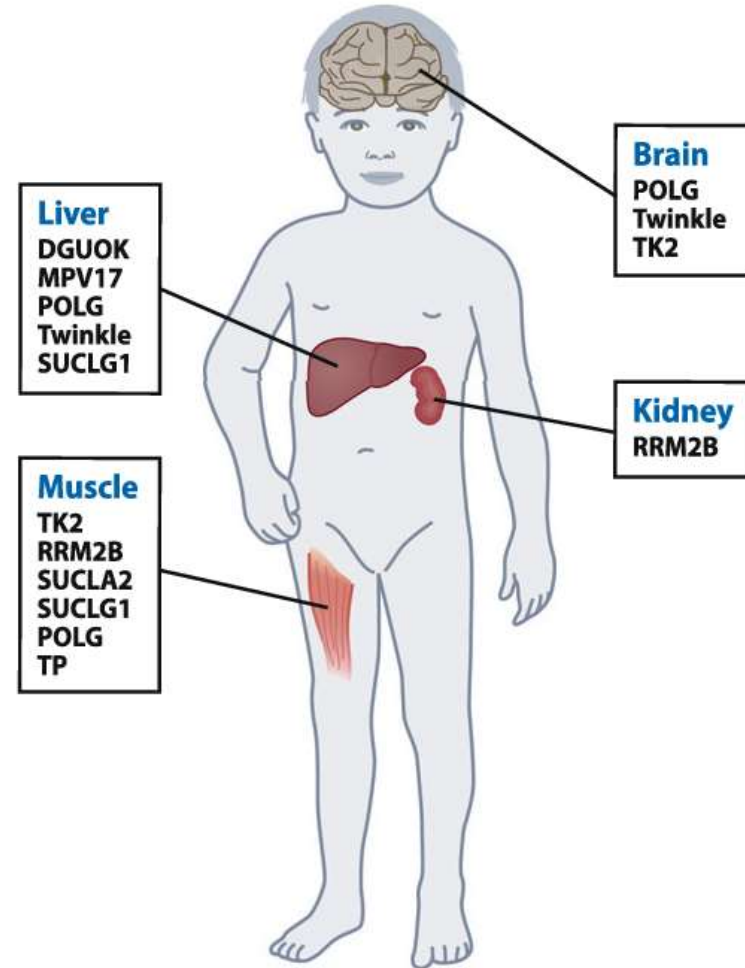
nDNA encoded deficiencies

mtDNA depletion syndromes

A. Signs and symptoms of MDS in different organs

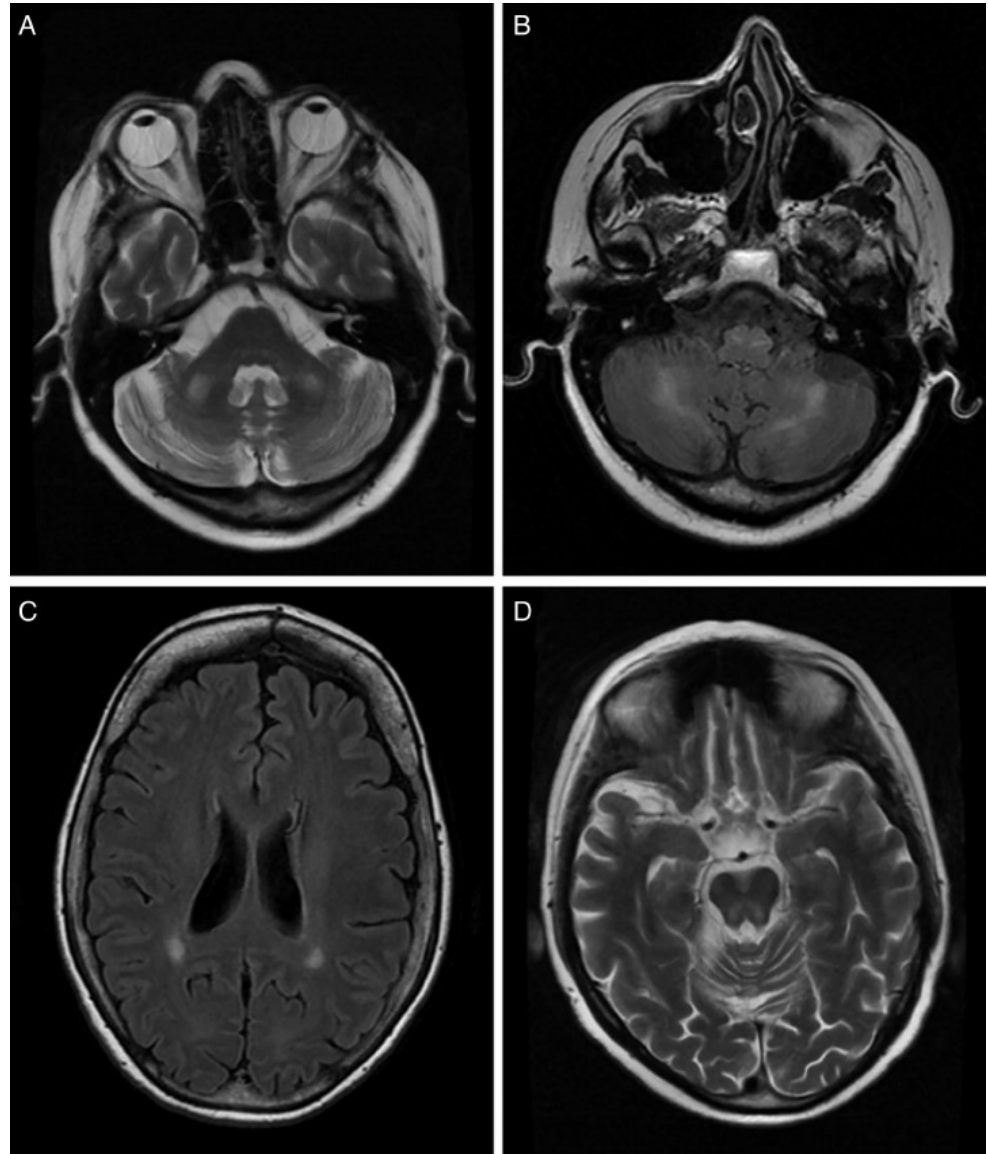


B. Tissues with identified MtDNA depletion



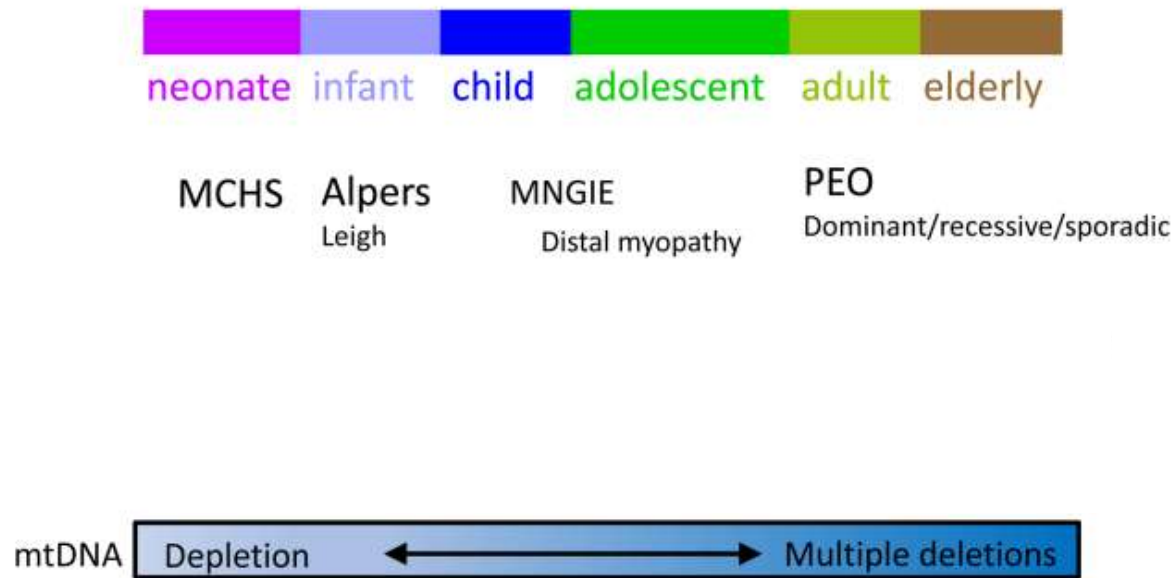


POLG deficiency

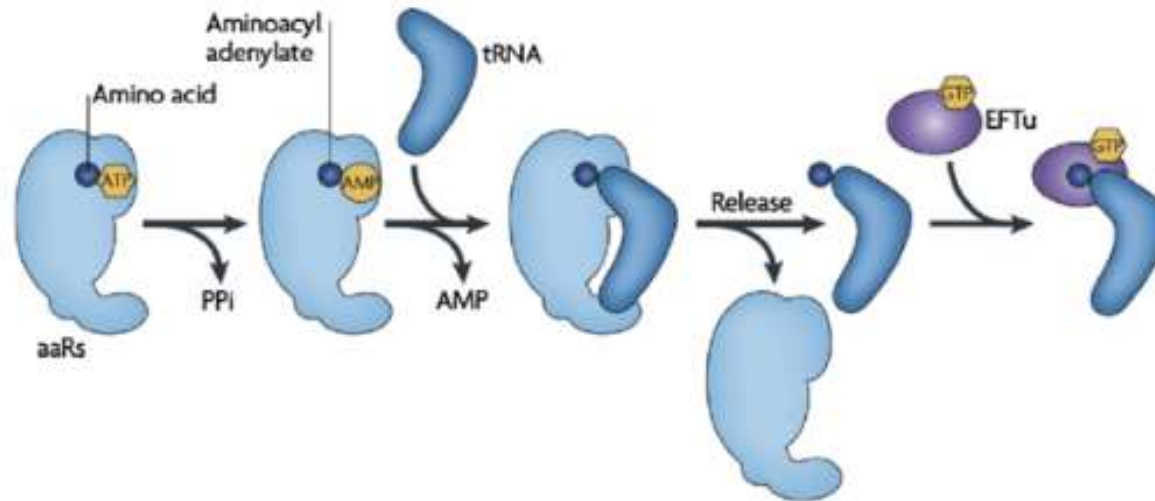


POLG-def: clinical spectrum

POLG mutations – clinical spectrum



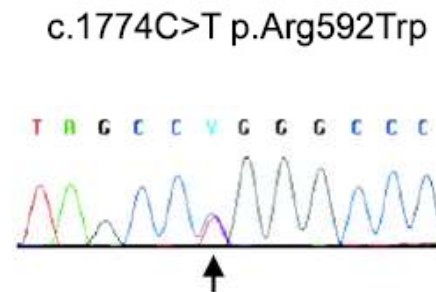
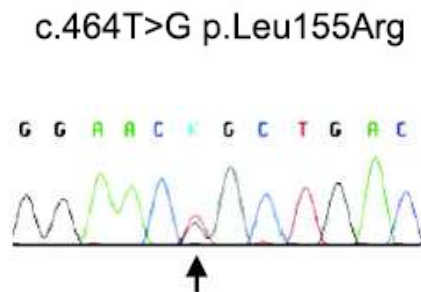
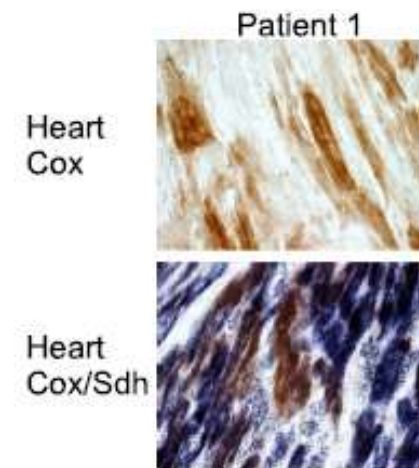
Amino-acyl tRNA synthetase deficiencies



AARS2-def

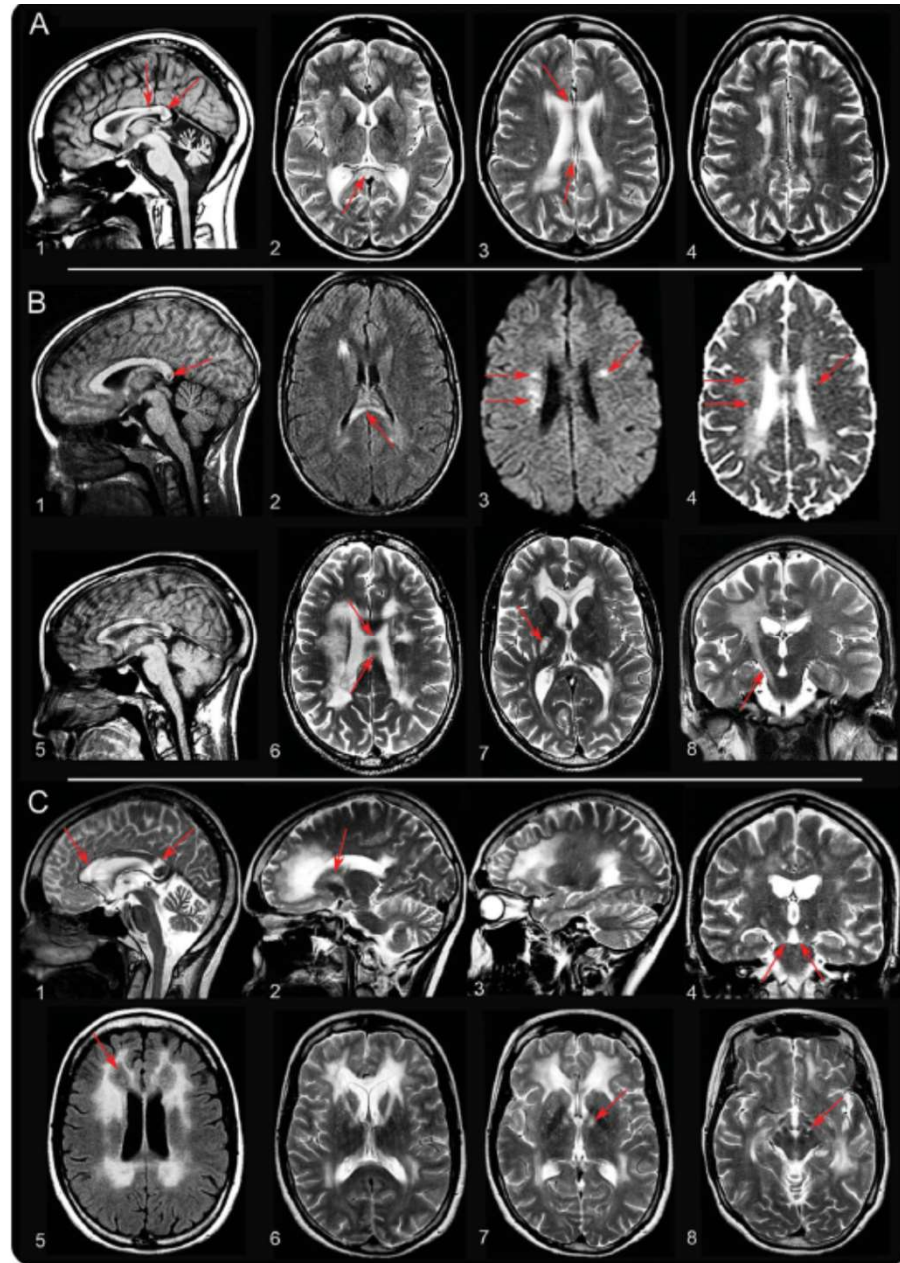
- hypertrophic cardiomyopathy
- Delayed motore development
- lactate

• ➔ WES: AARS2

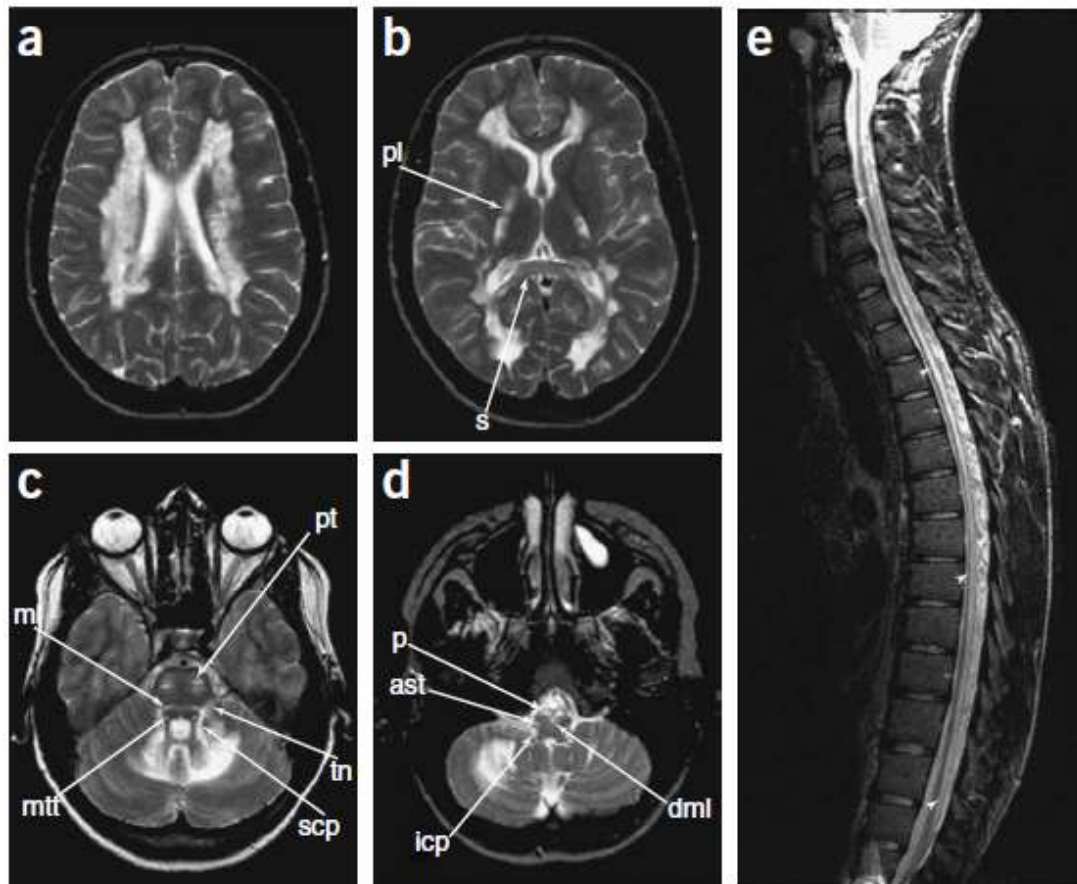


AARS2-def

- Progressive leuko-encephalopathie
- Ovarian failure
- NO cardiomyopathie



DARS2



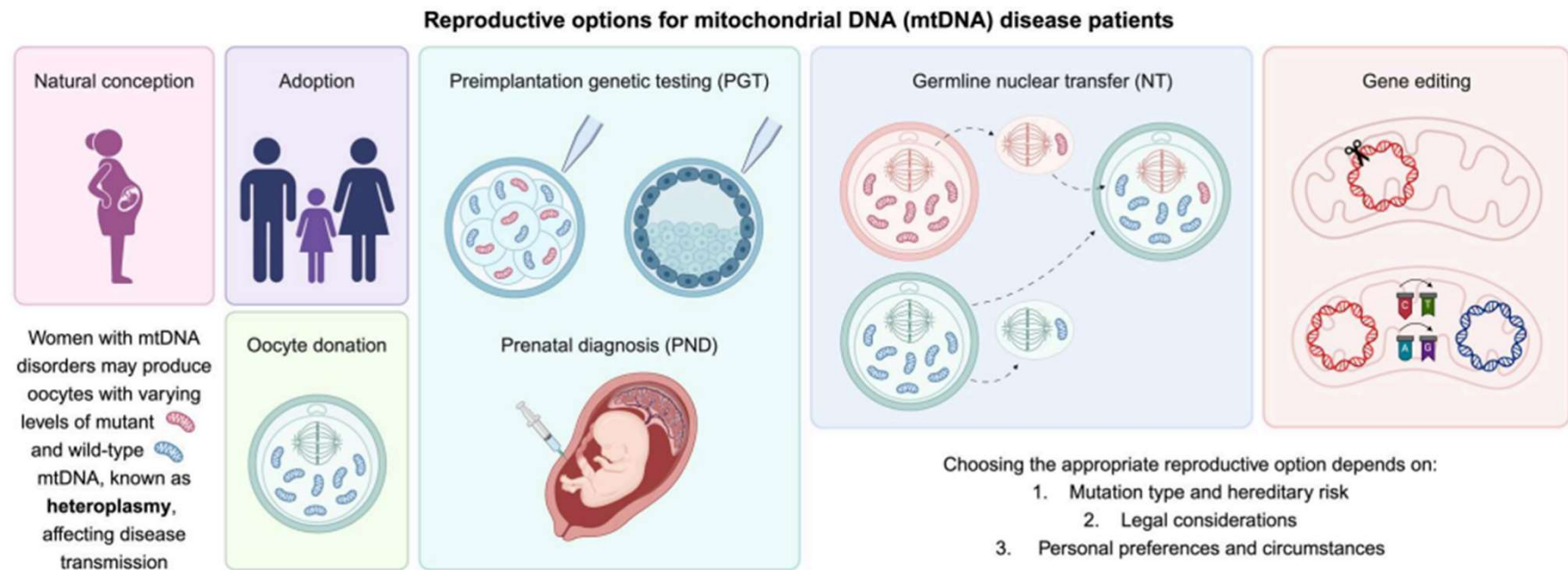
LBSL

Scheper et al., 2007

ADDENDUM: 2

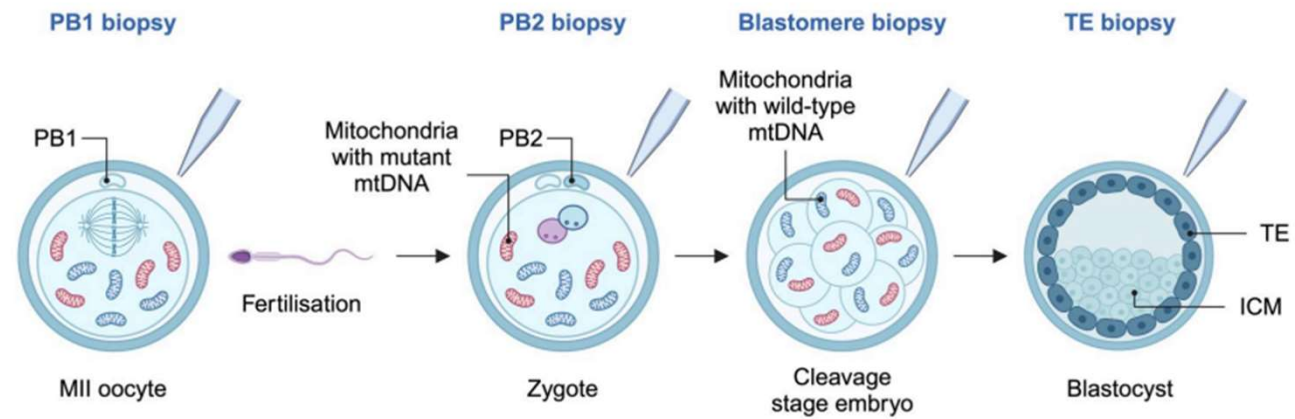
- Prevention of Mitochondrial diseases

Strategies to prevent



Strategies to prevent

A Preimplantation genetic testing (PGT)



B Prenatal diagnosis (PND)

