Človeški mitohondrij

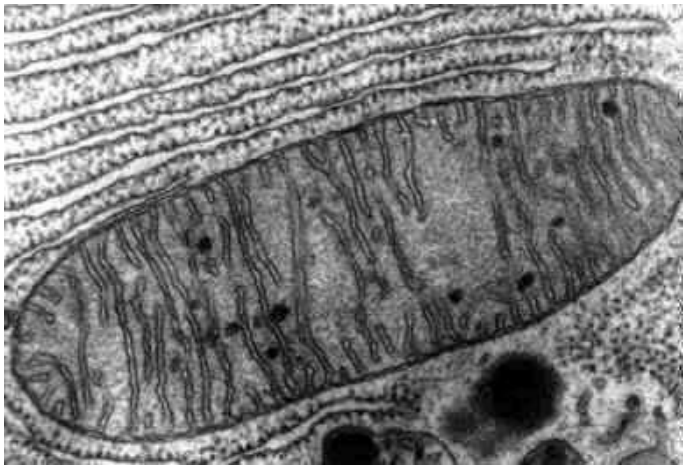
Boris Rogelj
Boris.Rogelj@ijs.si

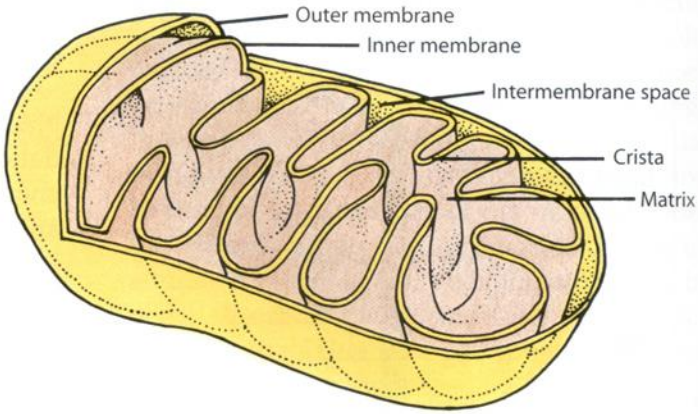
Pregled predavanja

- Osnove
- Nastanek mitohondrijev
- Funkcija
- Mitohondrijski genom
- Mitohondrijski transkriptom
- Genetika
- Mitohodrijske podatkovne baze
- Mitohondrijske bolezni

Uvod

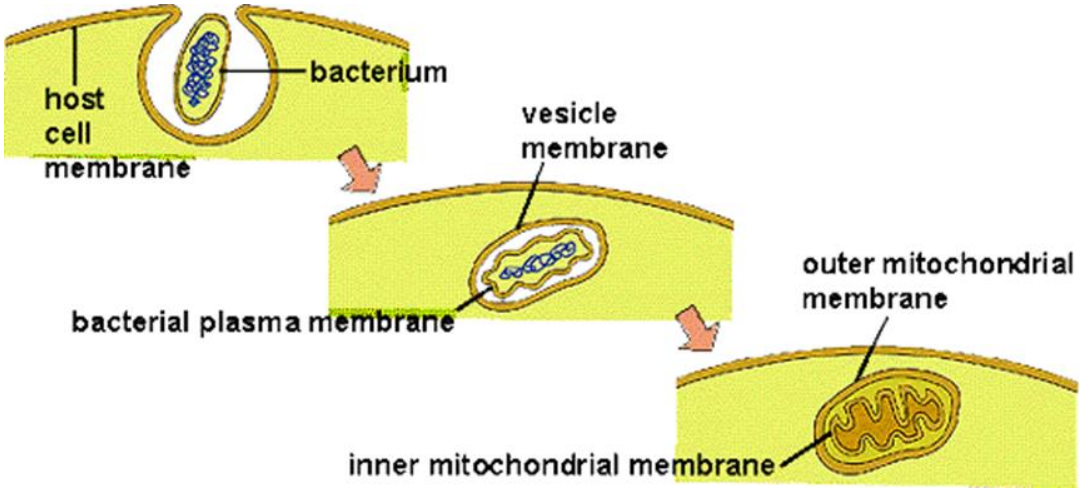
- Evkaronitske organele so obdane z membrano.
- Vse evkariontske celice imajo mitohondrije ali vsaj gene, ki izvirajo iz mitohondrijev.
- Mitohondrijev je nekaj sto do nekaj tisoč v vsaki celici.
- V njih poteka Krebsov cikel in oksidativna fosforilacija.
- Sestavni deli mitohondrija so:
  - Zunanja membrana
  - Notranja membrana (je nagubana in posledično ima večjo površino)
  - matriks (v tem delu so v plazmi matriksa procitske (krožne) molekule DNK in procitski ribosomi)
  - Medmembranski prostor





Teorija endosimbioze

- Prvotno jo je leta 1883 predlagal Andreas Schimper. Leta 1967 jo je dopolnila Lynn Margulis.



- Anaerobne bakterije (kisik je za njih toksičen) so internalizirale aerobne bakterije (potrebujejo kisik za preživetje). Obe sta pridobili prednost pri preživetju.

- V simbiontskem odnosu ima vsak partner določene vloge, koristne za oba partnerja. Aerobna bakterija ščitit anaeroba pred toksičnim kisikom, med tem ko anaerob hrani in varuje aerobnega simbionta.

- Končni rezultat = celica ima organel, obdan z dvojno membrano. Notranja membrana izvira iz celične membrane bakterije, zunanja membrana izvira od gostiteljske celice.

Teorija endosimbioze

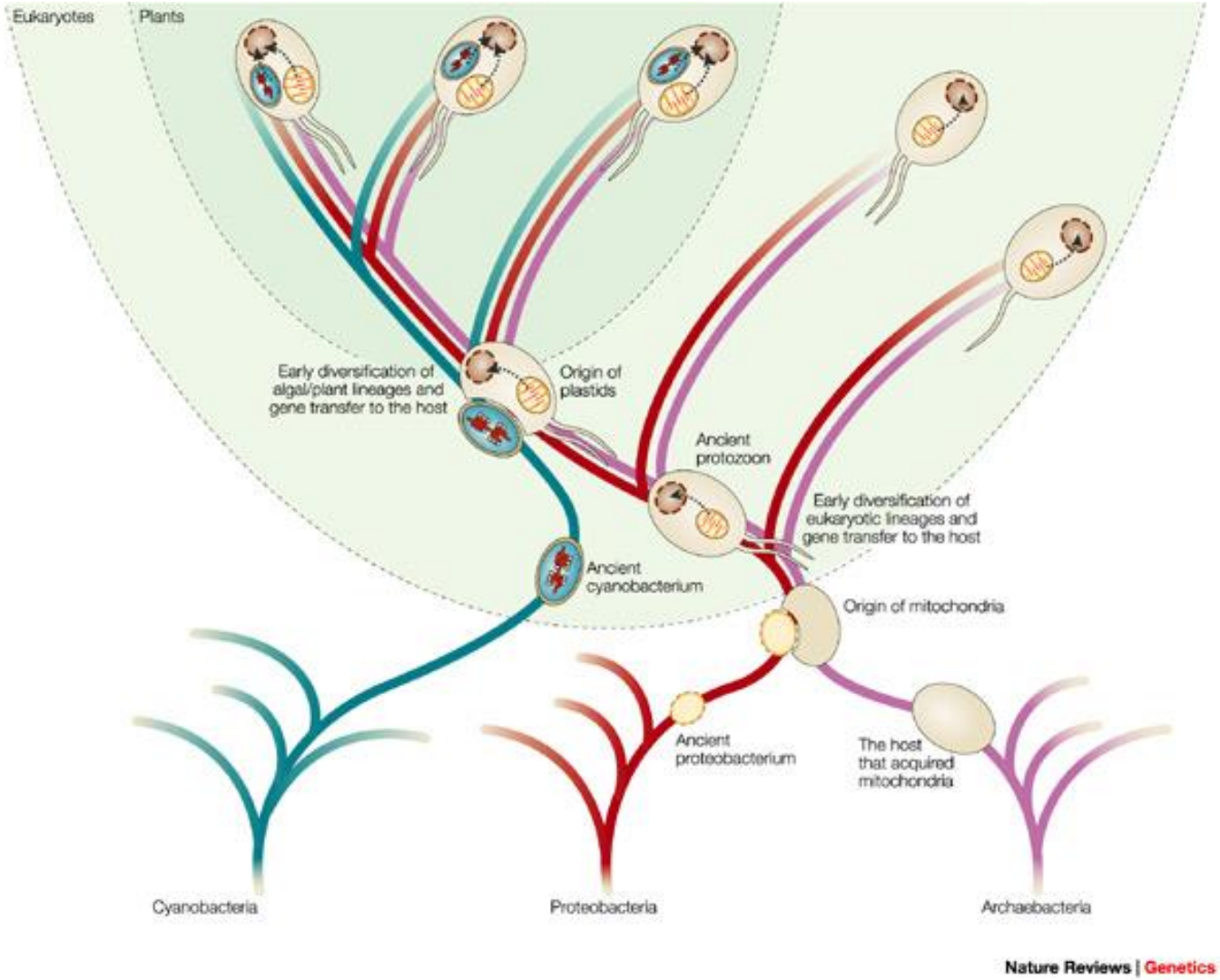
- Mitohondriji in skupina Rickettsia imata skupnega prednika.

- Dokazi za teorijo endosimibioze:
  - Mitohondriji imajo lastno DNA (krožno)
  - Notranja membrana je bolj podobna prokariontski.
  - Mitohondriji imajo svoje ribosome, ki so prokariontskega 70S tipa.
  - Mithondriji so občutljivi na neke bakterijske inhibitorje, ki ne vplivajo na evkariontske celice. Npr. streptomicin, kloramfenikol, rifampicin.
  - Sinteza proteinov pri mitohondrijih se začne z N-formil metioninom, tako kot pri bakterijah.

- Večina bakterijskih genov se je preselilo v jedro.
  - Protist *Reclinomonas americana* ima največji mt genom. Vse ostale mtDNA imajo samo del tega genoma. Drugi deli so ali prenešeni v jedro ali izbrisani.

- Evkarionti (Metamonade), ki nimajo mitohondrijev, imajo mitohondrijske gene v jedru. Torej so jih z evolucijo izgubili.

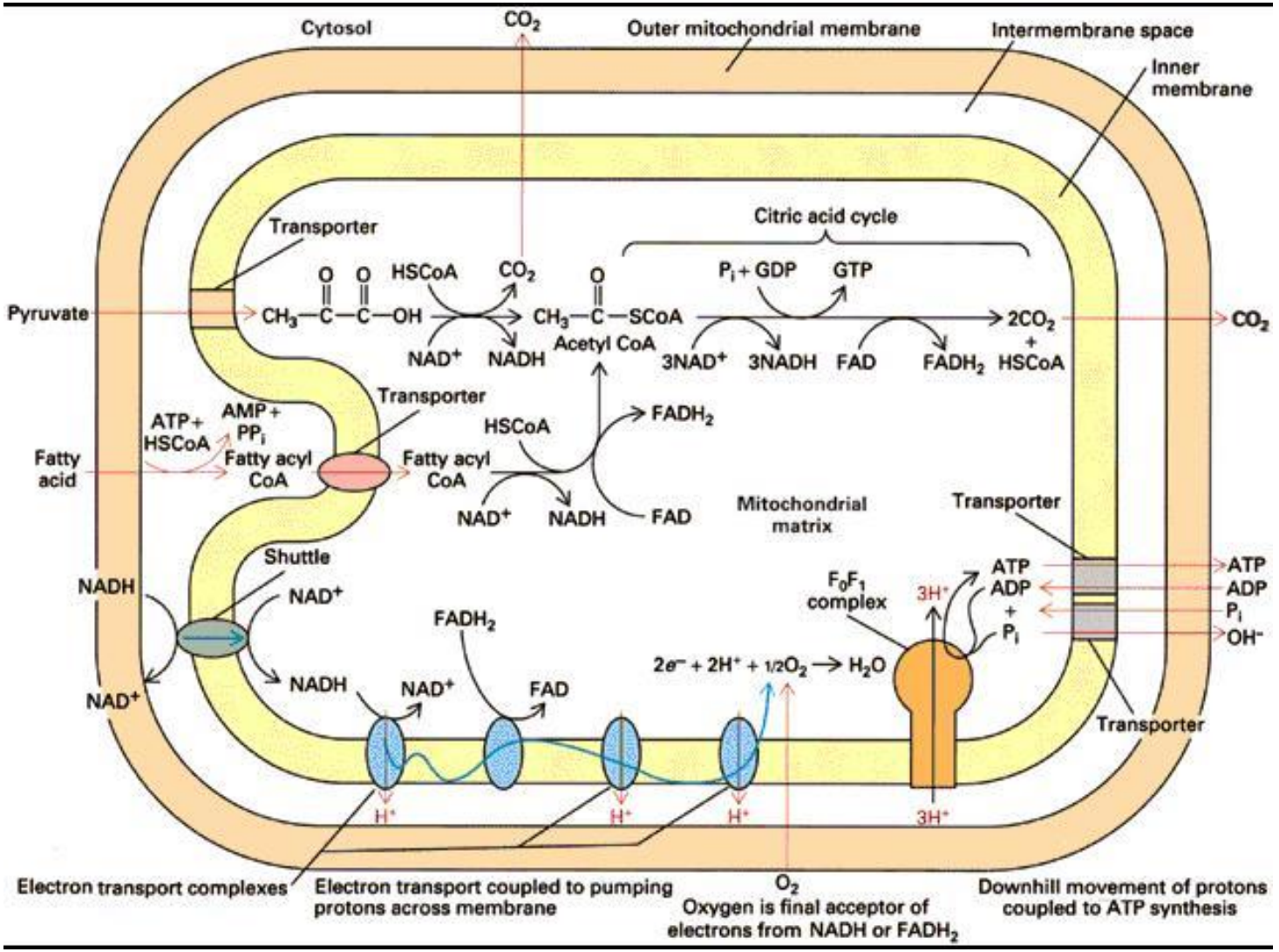
Teorija endosimbioze



Funkcija mitohondrijev

- Krebsov ciklus:
  - Piruvat, produkt glikolize, se tvori v citoplazmi.
  - Prenese se v mitohondrijski matriks.
  - V mm se pretvori v acetil CoA.
  - Maščobne kisline se tudi prenesejo v mm in se pretvorijo v acetil CoA.
  - V Krebsovem ciklu iz acetil CoA pridobimo CO2 in visoko energetske elektrone, ki so vezani na NADH in $FADH_{2.}$
- Transportna veriga elektronov:
  - NADH in $FADH_2$ preneseta eletrone na tri proteinske komplekse, vsidrane v notranji membrani.
  - Vsak kompleks uporabi enegijo elektronov pri črpanju H^+ ionov iz matriksa v medmembranski prostor.
  - Tretji kompleks prenese elektrone na kisik in tvori vodo.
  - Skozi četrti kompleks (ATPaza) H^+ ioni pridejo nazaj v matriks. Pri tem pride do tvorbe ATP iz ADP in fosfata.
- V rjavem maščevju potujejo protoni nazaj v matriks skozi protein termogenin, pri tem se sprošča toplota.

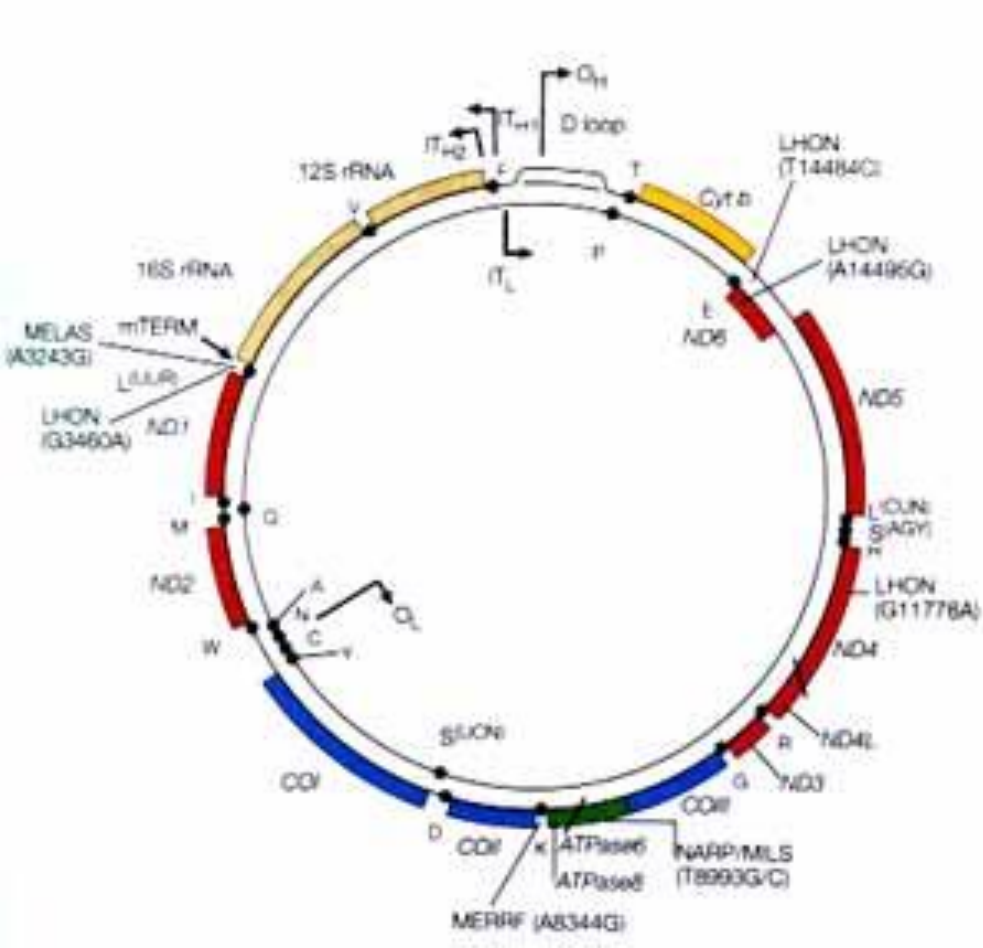
Funkcija mitohondrijev



Struktura mitohondrijskega genoma

- Človeški mitohondrij je 16,6kb dolga krožna DNA.
- 44% (G+C)
- Verigi mtDNA sta opazno različni glede na razmerje baz, ki ju sestavljata.
- Vodilna/težka veriga (H-strand) je bogata z gvaninin.
- Druga/lahka (L-strand) je bogata s citozini.
- Obe verigi nosita zapise za gene.
- Intronov ni.
- Gene so dobro pakirani – skoraj ni nekodirajočih delov razen v zanki D. V nekaterih primerih celo pride do delnega prekrivanja.

- En mitohondrij ima več kopij mtDNA.



Prekrivanje genov

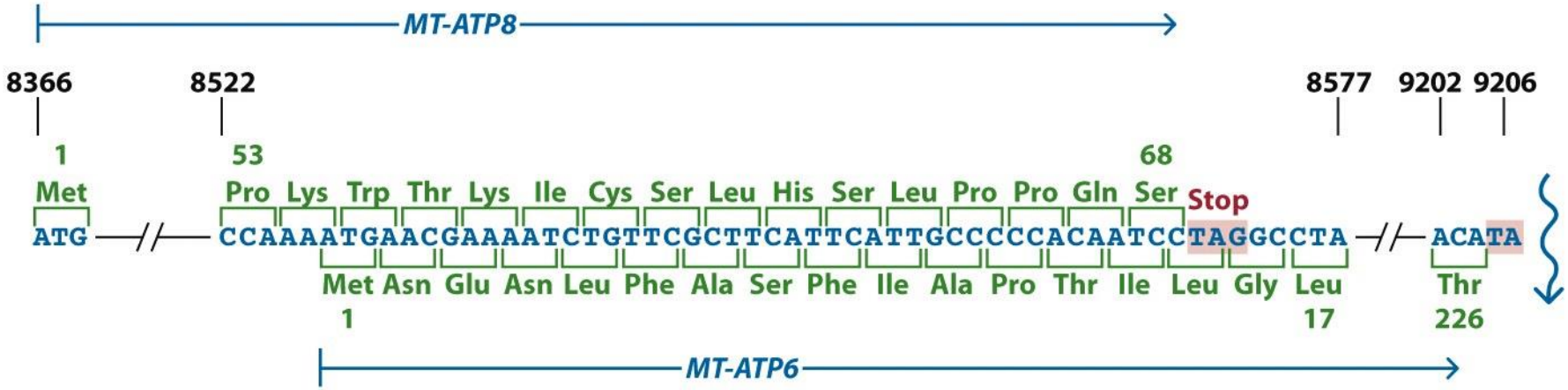


Figure 9.4 Human Molecular Genetics, 4ed. (© Garland Science)

- MT-ATP8 in MT-ATP6 sta prepisana iz različnega bralnega okvirja.
- Po transkripciji se RNA, ki nosi zapis za ATP sintazo 6, reže na mestu 9206 in poliadenilira.
- Pride do tvorbe stop kodona UAA, kjer je zadnji nukleotid prvi nukleotid poli(A) repa.

Razlika v velikosti med jedrnim in mitohondrijskim genomom

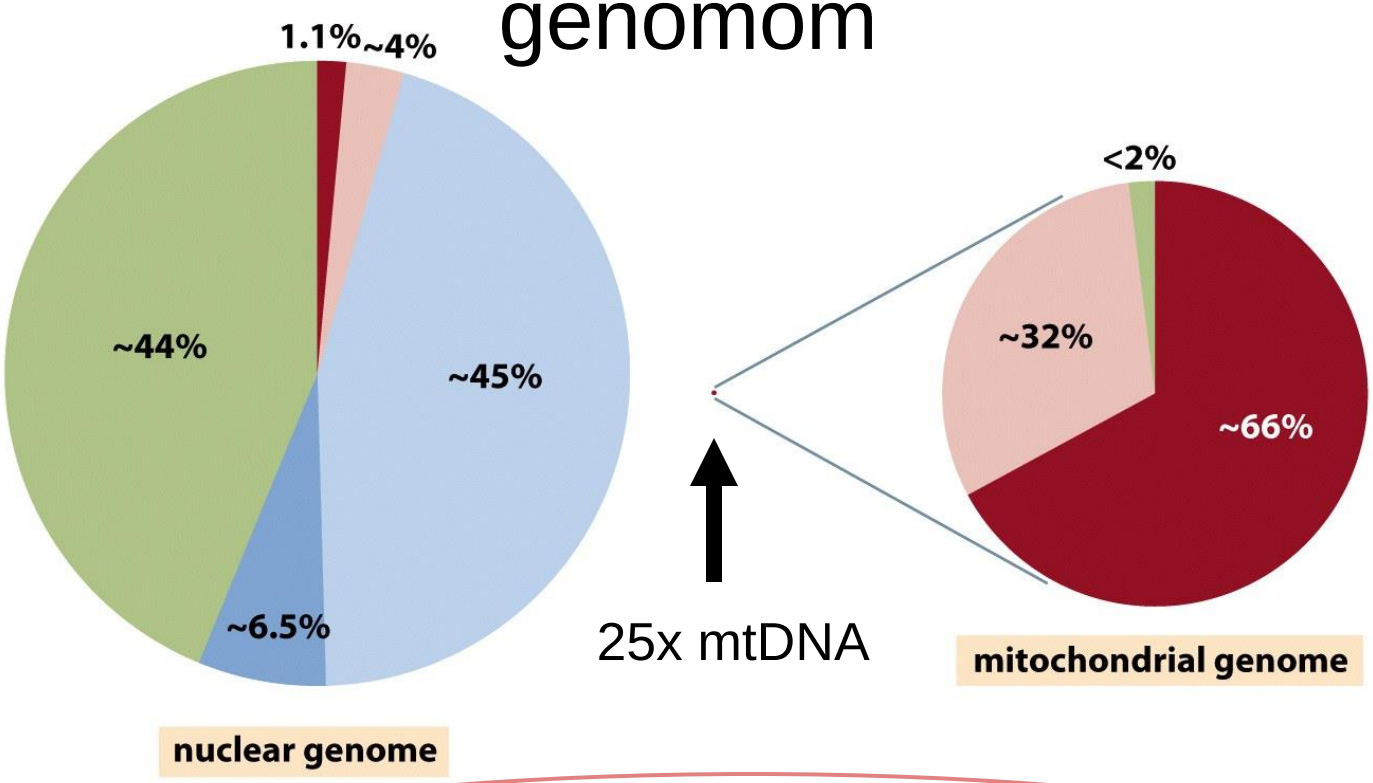


Figure 9.1 Human Molecular Genetics, 4ed. (© Garland Science)

Geni mitohondrijev

- Število genov: 37
  - 22 tRNA
  - 2 rRNAs
  - 13 polipeptidov.

- tRNA: 60 od 64 kodonov kodira aminokisline. 8 tRNA pokriva vse aminokisline, ki imajo na tretjem mestu vse baze. 14 tRNA pokriva po dva kodona (purini ali pirimidini na tretjem mestu).
  - 8x4+14x2=60

- rRNA: 16S in 12S

- Proteini: vsi so sestavni deli elektron transportne verige. Zapisi za ostale proteine so v jedru.

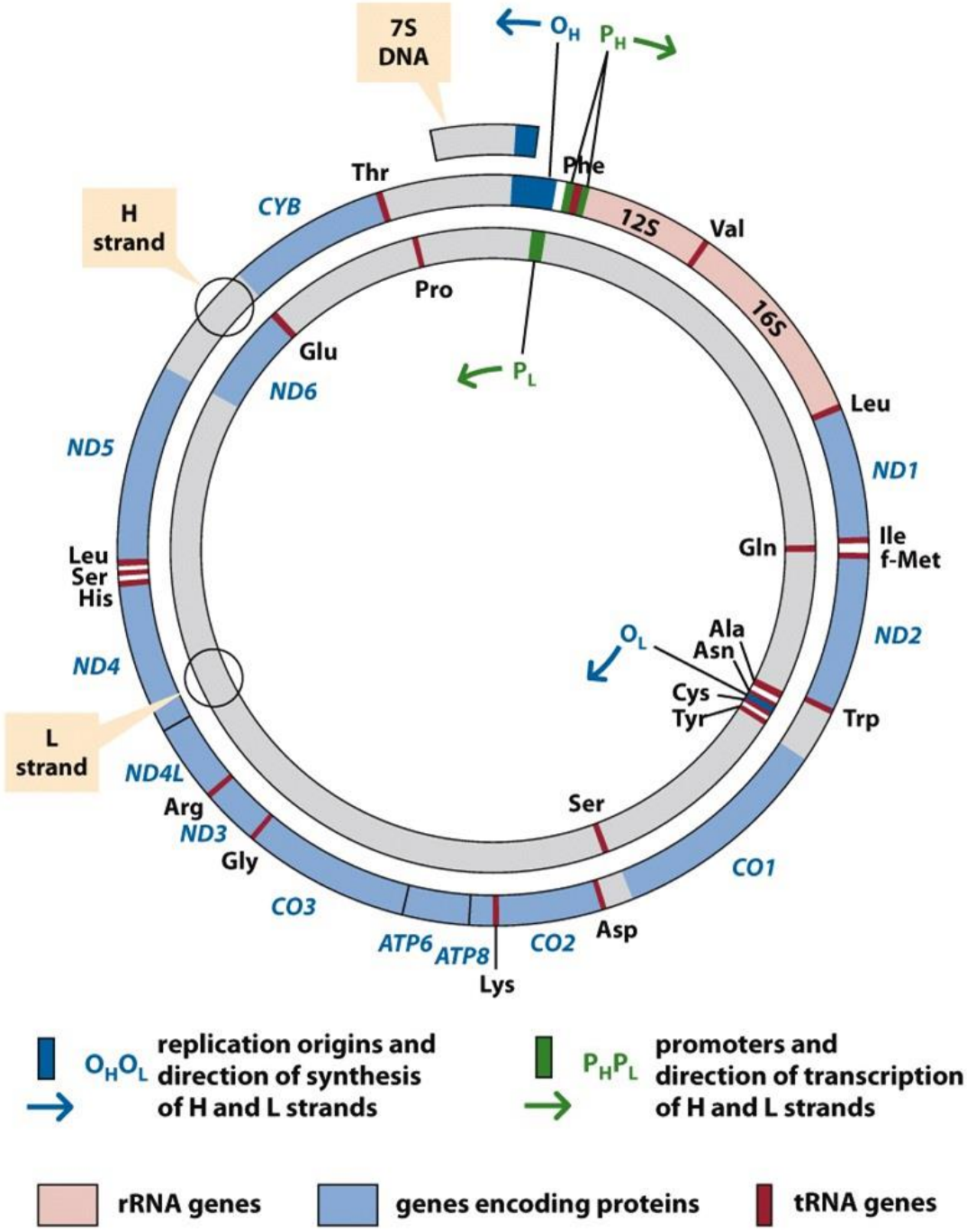


Figure 9.3 Human Molecular Genetics, 4ed. (© Garland Science)

TABLE 9.1 THE LIMITED AUTONOMY OF THE MITOCHONDRIAL GENOME

Mitochondrial component	Encoded by	
	Mitochondrial genome	Nuclear genome
Components of oxidative phosphorylation system	**13 subunits**	**80 subunits**
I NADH dehydrogenase	7	42
II Succinate CoQ reductase	0	4
III Cytochrome b–c_1 complex	1	10
IV Cytochrome c oxidase complex	3	10
V ATP synthase complex	2	14
Components of protein synthesis apparatus	**24 RNAs**	**79 proteins**
rRNA	2	0
tRNA	22	0
Ribosomal proteins	0	79
Other mitochondrial proteins	**0**	**All[a]**

[a]Includes mitochondrial DNA and RNA polymerases plus numerous other enzymes, structural and transport proteins, etc.

Table 9.1 Human Molecular Genetics, 4ed. (© Garland Science)

Replikacija mitohondrijske DNA

- Replikacija se začne na H verigi.
  - Začetek replikacije H verige je na D zanki (O_H). Iniciacija je z RNA začetnim oligonukleotidom, ki izhaja iz transkripta L verige.
  - Začetek replikacije L verige (O_L) se odkrije, ko je nova H veriga približno 2/3 dokončana. Začetek replikacije L verige je na stari H verigi. O_L se odkrije, ko DNA polimeraza, ki sintetiziran novo H verigo, odmakne staro H verigo.
  - Originalna L veriga se zvije v zanko, ki deluje kot začetni oligonukleotid in replikacija L verige se začne.
  - Replikacija je bidirekcionalna in asinhrona, za razliko od jedrne DNA, ki se v obeh smereh podvojuje hkrati.

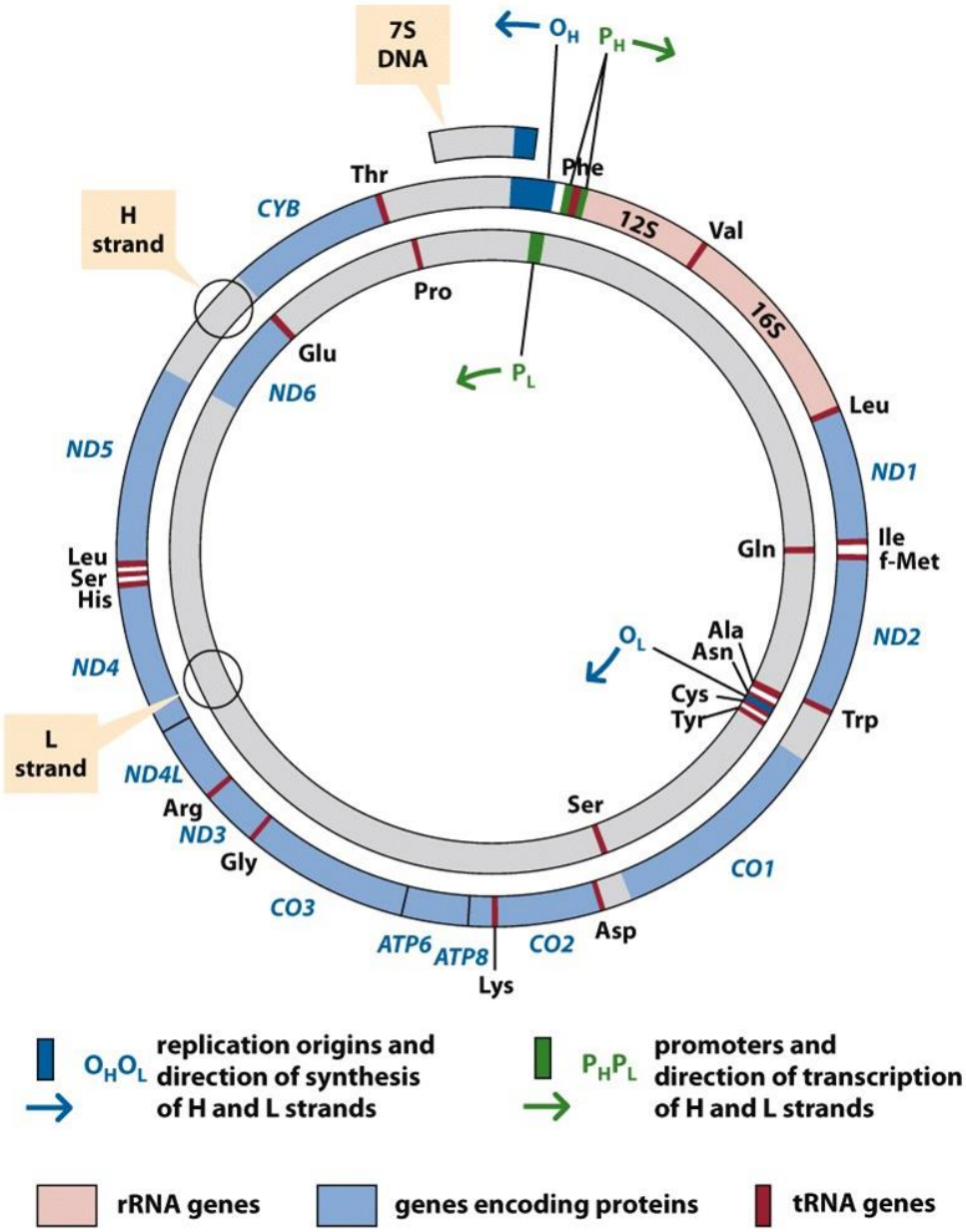


Figure 9.3 Human Molecular Genetics, 4ed. (© Garland Science)

D zanka

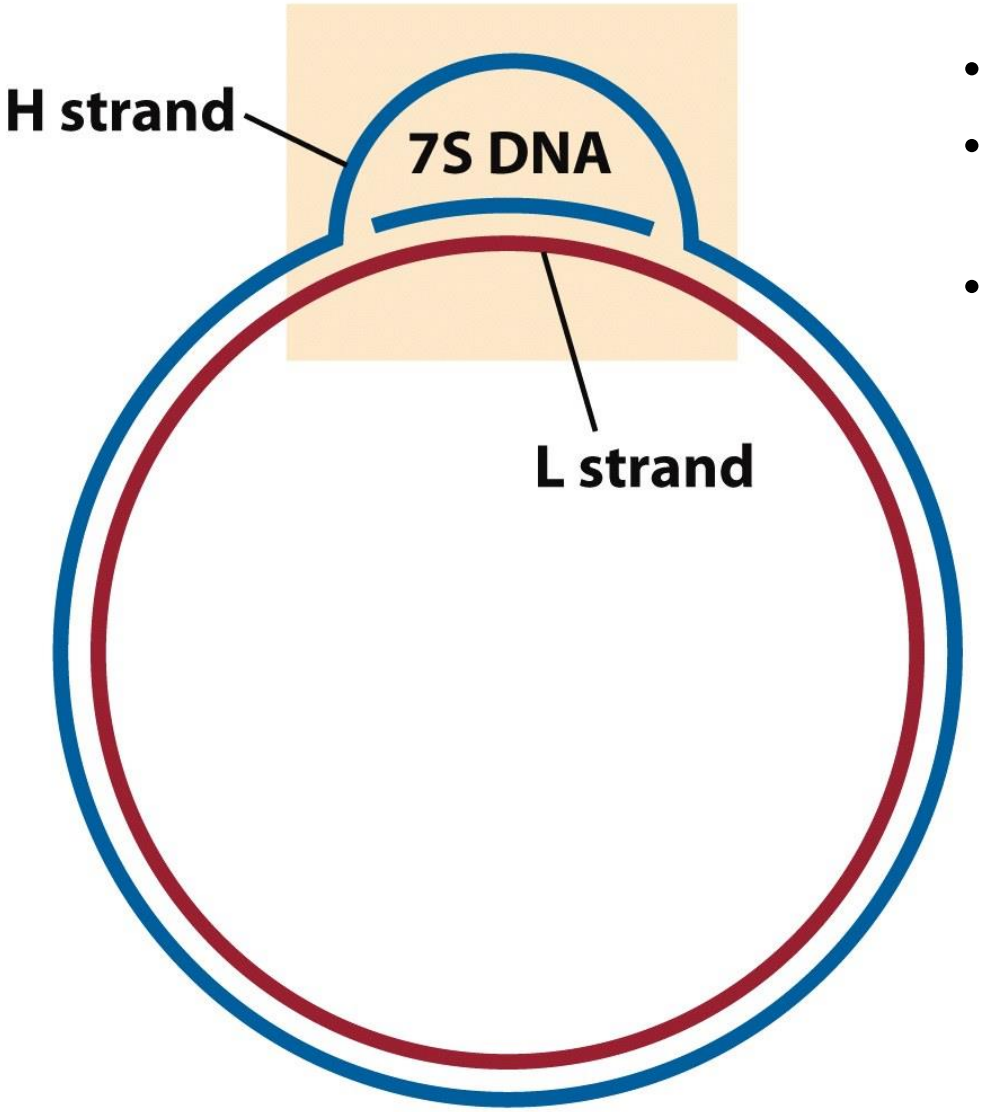
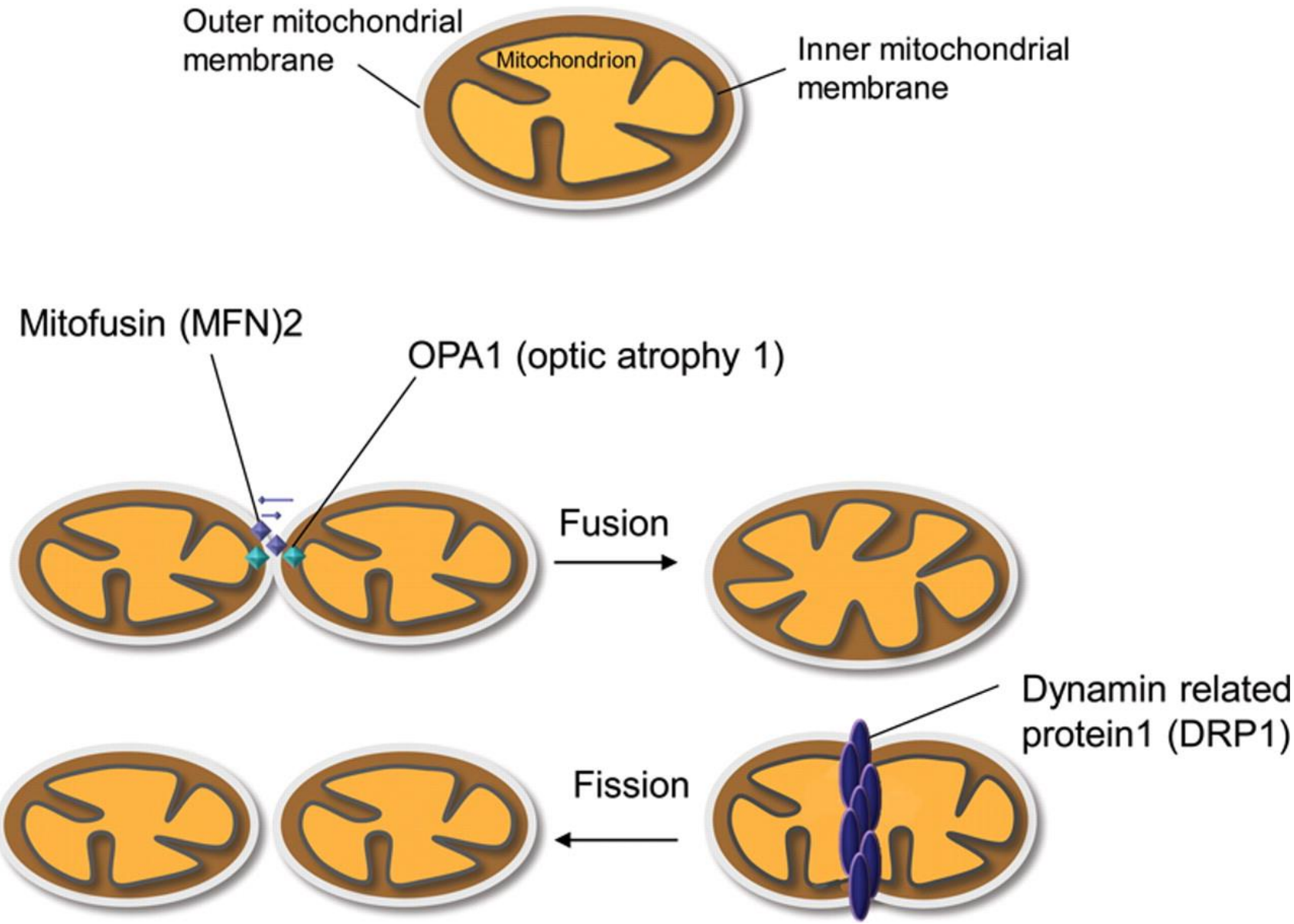


Figure 9.2 Human Molecular Genetics, 4ed. (© Garland Science)

- Kratko zaporedje (1121 bp)
- Tvori se trojni heliks. Nastaneta dve kopiji H verige.
- To je kontrolna regija za večino replikacij in transkripcij.

Delitev in združevanje mitohondrijev



Genetski kod mitohondrijev

- Genetski kod mitohondrijev je rahlo drugačen od univerzalnega koda.
- Uporablja 4 stop kodone.
- UGA v mitohondrijih kodira triptofan, drugače je stop kodon v univerzalnem kodu.
- AUA v mitohondrijih kodira metionin namesto izolevcina.

First letter	Second letter				Third letter
	U	C	A	G	
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	*Stop*	*(Stop)* Trp	A
	Leu	Ser	*Stop*	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile (Met)	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	(Ile) Met	Thr	Lys	(Arg) *Stop*	A
	Met	Thr	Lys	(Arg) *Stop*	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

Mitohondrijski transkriptom

Primarni mitohondrijski transkripti

- Prepišejo se tri policistronske verige:
  - Celotna težka veriga
  - Celotna lahka veriga
  - Del težke, ki kodira rRNA
- Model z ločili:
  - Med posameznimi transkripti so tRNA geni. Z izrezovanjem tRNA se izrežejo tudi mt mRNA
- Variabilnost izražanja:
  - V srcu je mt mRNA 30 % totalne mRNA
  - V tkivih z manjšo energetsko zahtevnostjo pa 5 %
- Variabilnost med posameznimi transkripti se doseže s:
  - Procesiranjem
  - Stabilnostjo
  - Razgradnjo

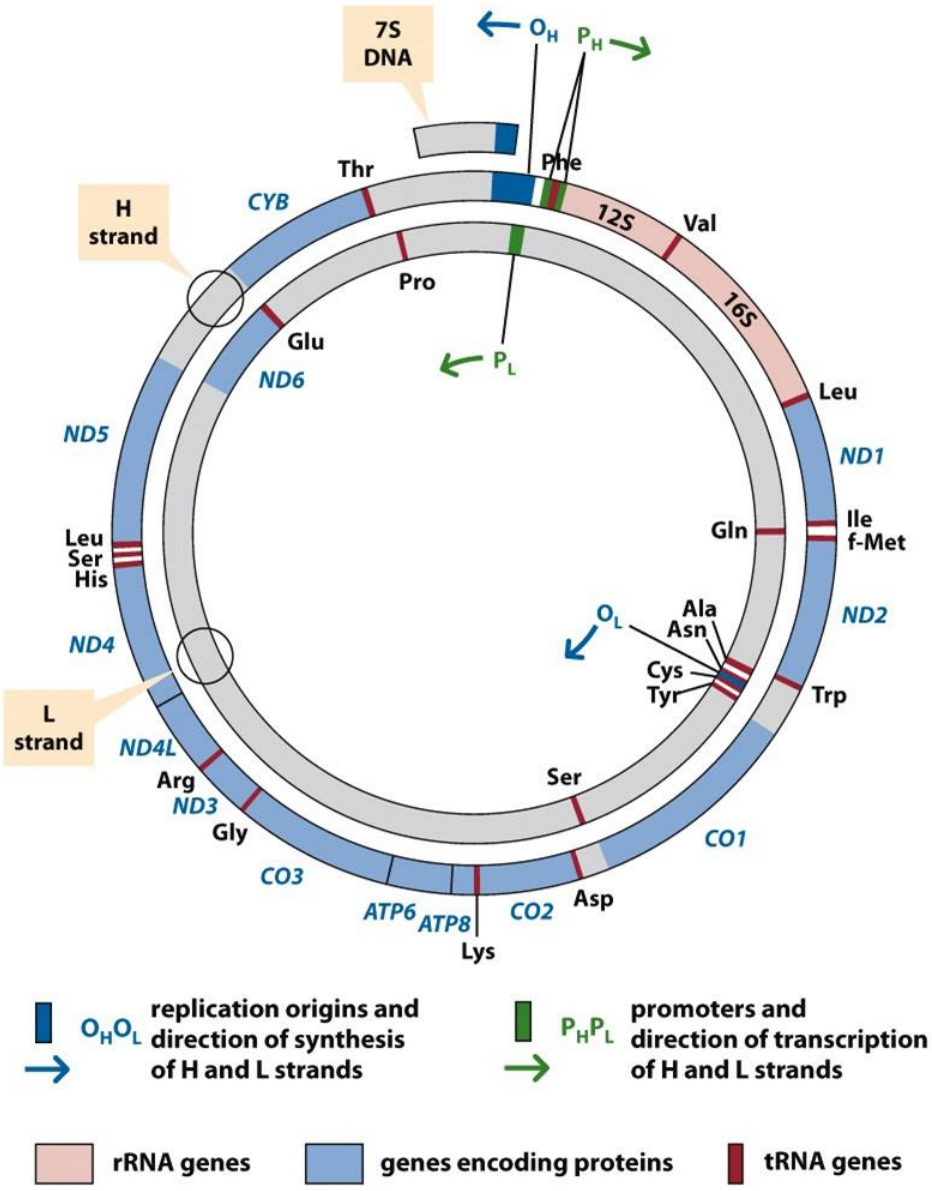
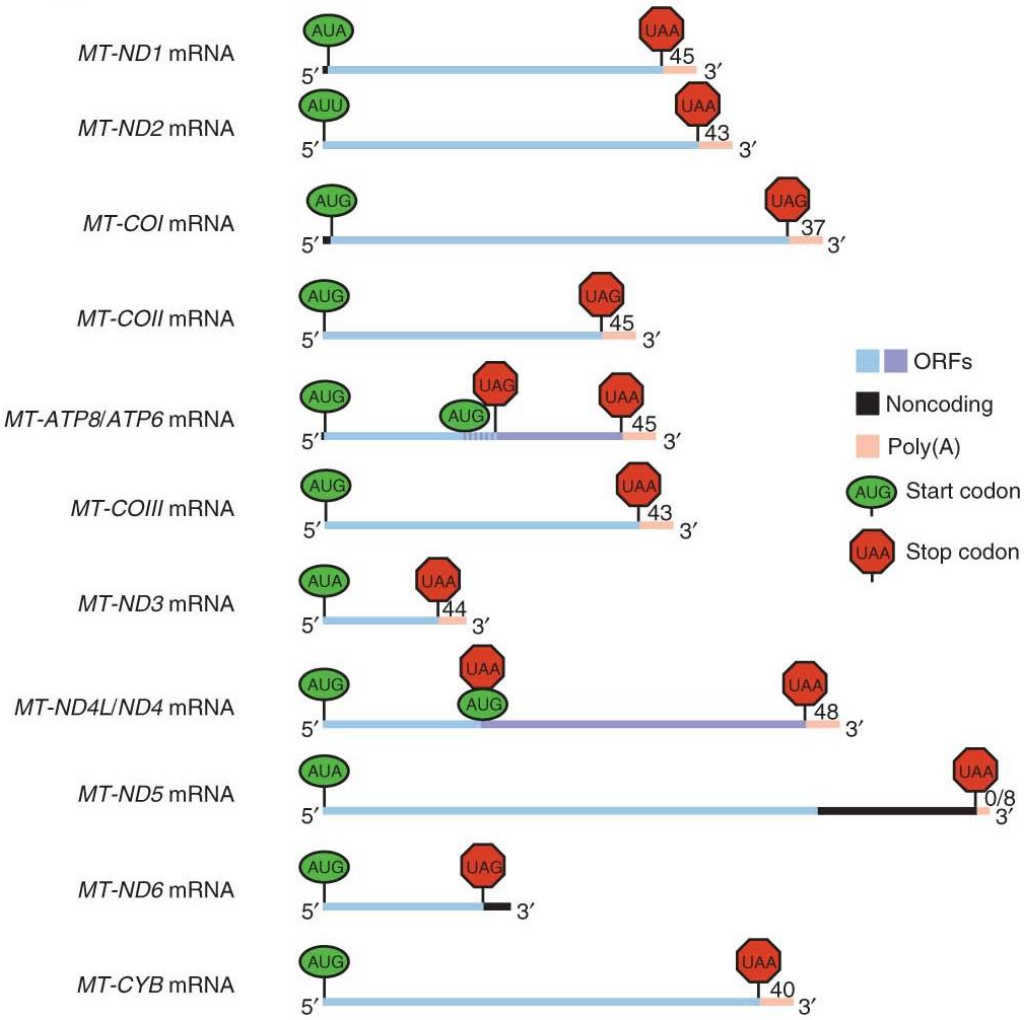


Figure 9.3 Human Molecular Genetics, 4ed. (© Garland Science)

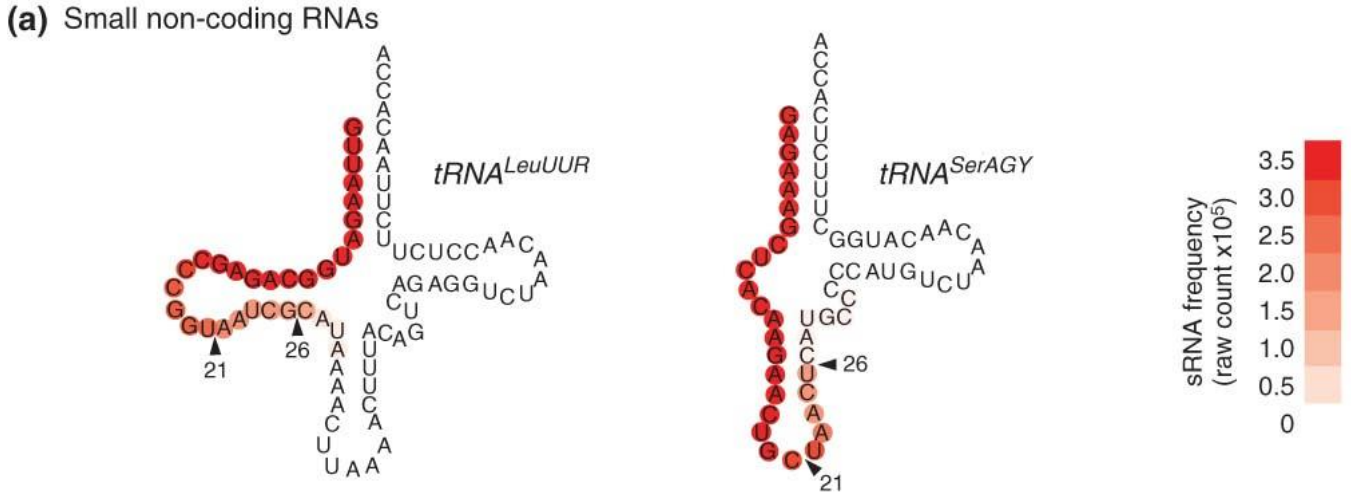
Procesirane mt mRNA

- Mt mRNA nimajo klasičnih 5‘ in 3‘ UTR, intronov, 5‘ metil gvanozinske kape ali modificiranih baz.
- Večina mt mRNA se začne s start kodonom na 5‘koncu. (3 izjeme z 1, 2 ali 3 nt pred startom)
- Vse mt RNA (razen ene MT-ND6) imajo poli(A) rep:
  - 7 jih uporablja poli(A) rep kot del STOP signala.
- V nekaterih so v 3‘UTR močne sekundarne strukture, ki so pomembne pri terminaciji sinteze proteinov.



DOI: 10.1002/wrna.1128

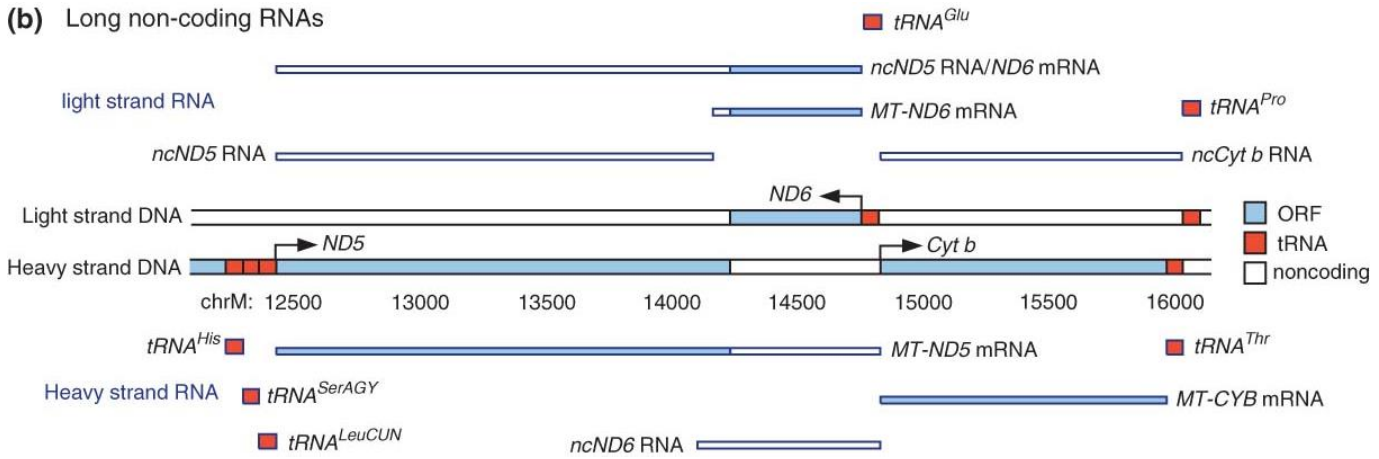
Male mt ncRNA



- Male nekodirajoče RNA nastanejo iz $tRNA^{LeuUUR}$ in $tRNA^{SerAGY}$. Frekvenca velikosti malih RNA je predstavljena z odtenki rdeče: zaporedje so določili iz izbranih RNA knjižnjic iz mitohondrijev 143B osteosarkoma celic.

DOI: 10.1002/wrna.1128

Dolge mt ncRNA



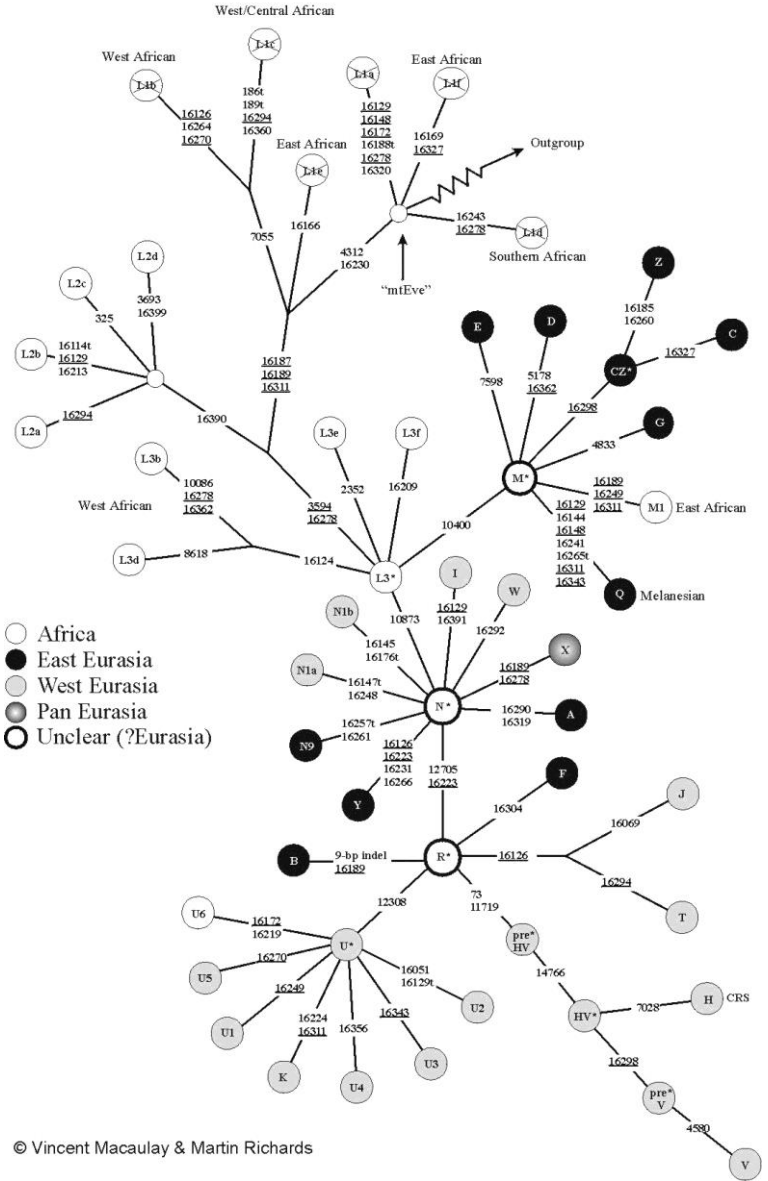
- Dolge mitohondrijske nekodirajoče RNA nastanejo iz ND5, ND6, Cyt b regij iz mitohondrijskih genomov – prikazano skupaj z mRNA in tRNA iz iste regije.

DOI: 10.1002/wrna.1128

Analiza mitohondrijske DNA

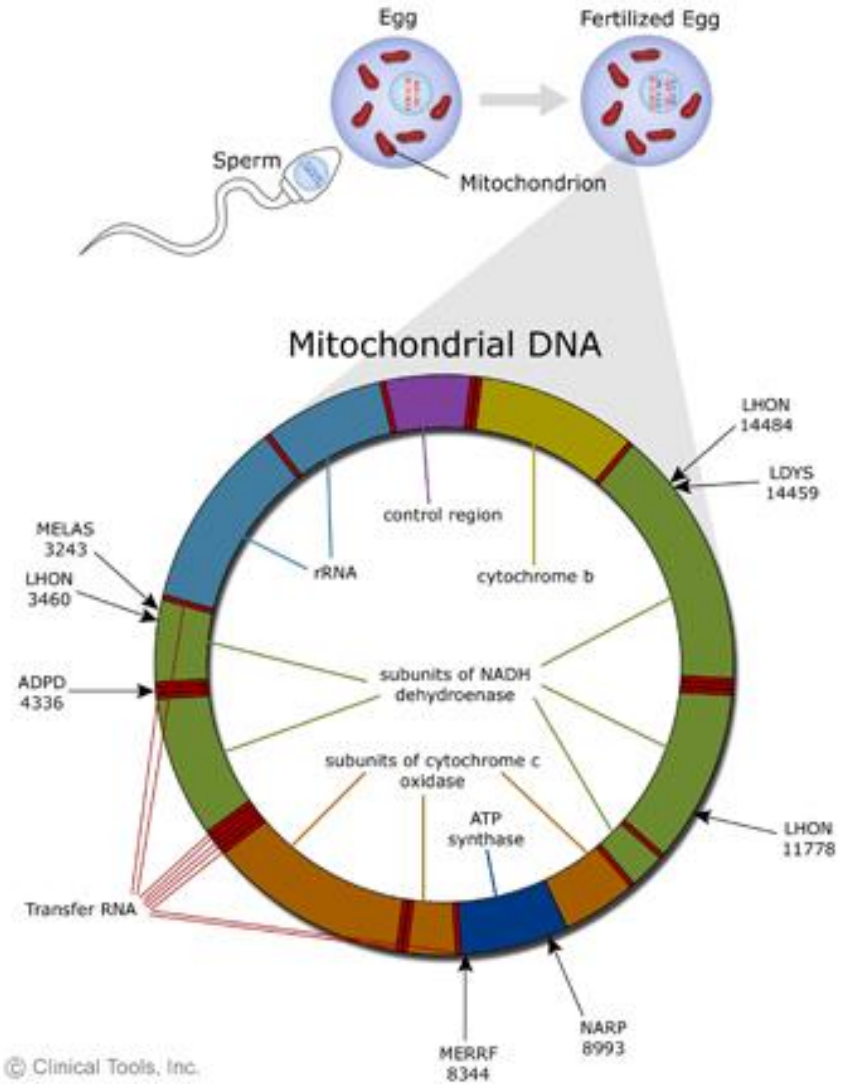
Mitohondrijska genetika

- Materinsko dedovanje: deduje se samo po materinski liniji (jajčna celica). Omogoča sledenje ženskih prednikov.
- Mitohondriji iz spermijev (če sploh so) se hitro razgradijo. V redkih primerih se prenese tudi očetov mitohondrij.
- Hitrost nastajanja novih mutacij je 10x hitrejša od jedrnega genoma. mtDNA je vezana na notranjo membrano, kjer poteka oksidativna fosforilacija. Produkti, ROS, so zelo mutageni. Najhitreje pride do mutacij na zanki D.
- Staranje se prepisuje tudi postopnemu zmanjšanju in izgubi mitohondrijev zaradi kopičenja mutacij v posameznih celicah.



Analiza mitohondrijske DNA

- Mitohondrijski genom= 16,569 bp.
  - 530 variabilnih mest pri človeku.
- D-zanka- kontrolno mesto
  - Hipervaribilno zaporedje 1 (HVS 1)
    - 16024-16383 (360 bp).
    - 240 variabilnih mest pri HVS 1.
    - Variacija je med 0-20 bp.
    - V povprečju osebki med sabo variirajo za 8 bp.
  - Hipervaribilno zaporedje 2 (HVS 2)
    - 73-340 (268 bp).
    - 117 variabilnih mest pri HVS 2.
    - Variacija je med 0-10 bp.
    - V povprečju osebki med sabo variirajo za 2 bp.
- Zakaj uporabljat HSV 1 in HSV 2?
  - So zelo variabilne.
  - Večje število kopij/celica (200-10,000).
  - Dobre za analizo majhnih ali degradiranih vzorcev.
  - Velike podatkovne baze s svetovnimi variacijami, ki se lahko uporablja za primerjavo in analizo.



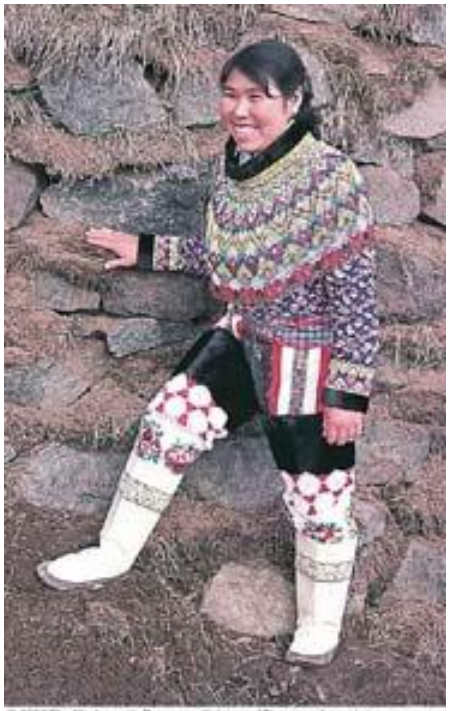
Mitohondrijske haploskupine

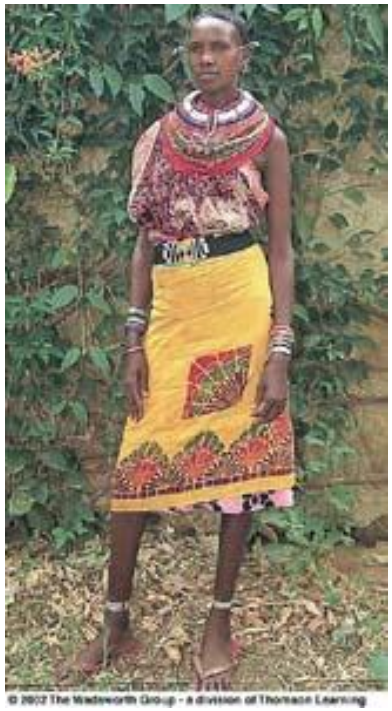
- Haploskupina - materinska ali očetovska genetska zasnova osebka.
  - Do sedaj je definiranih 18 haploskupin.
    - Opisanih je še več dodatnih podskupin.
- Poimenovanje skupine – zasnovano na spremembah v zapisu zaporedja HSV1. Lahko se uporabi tudi HSV 2 ali SNPji s celega mt genoma.
  - Cambridge Reference Sequence (CRS).

Haplogroup	HVS-I motif
L1a	148 172 187 188G 189 223 230 311 320
L1b	126 187 189 223 264 270 278 311
L1c	129 187 189 223 278 294 311 360
L1e	129 148 166 187 189 223 278 311
L1f	169 187 189 223 230 278 311 327
L2	223 278 *390*
L3	223
>L3b	124 223 278 362
>L3d	124 223
>L3e	223
>M	223
>>M1	129 189 223 249 311
>>C	223 298 327
>>D	223 362
>>E	223 227 362
>>G	*017* 129 223
>>Z	185 223 224 260 298
>N	223
>>N1	223
>>>N1a	147A/G 172 223 248 355
>>>N1b	145 176G 223
>>>N1c	223 265
>>>I	129 223 *391*

>>>I	129 223 *391*
>>A	223 290 319
>>W	223 292
>>X	189 223 278
>>R	CRS
>>>R1	278 311
>>>R2	*071*
>>>B	189
>>>F	304
>>>Y	126 231 266
>>>JT	126
>>>>J	*069* 126
>>>>>J1	*069* 126 261
>>>>>>J1a	*069* 126 145 231 261
>>>>>>J1b	*069* 126 145 222 261
>>>>>>>J1b1	*069* 126 145 172 222 261
>>>>>J2	*069* 126 193
>>>>T	126 294
>>>>>T1	126 163 186 189 294
>>>>>T2	126 294 304
>>>>>T3	126 292 294
>>>>>T4	126 294 324
>>>>>T5	126 153 294
>>>U	CRS
>>>>U1	249

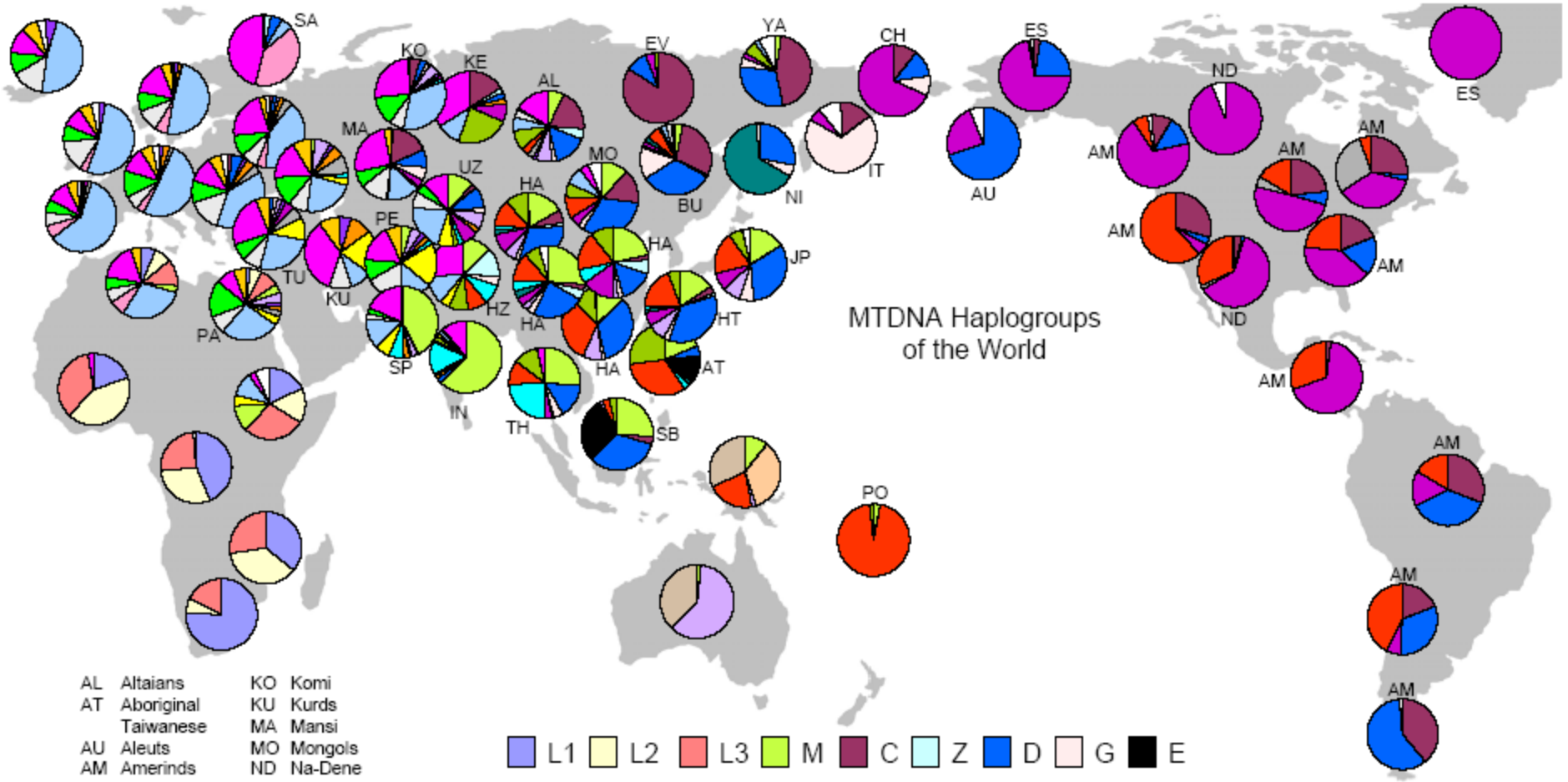
>>>>U1	249
>>>>>U1a	189 249
>>>>>U1b	249 327
>>>>U2	*051* 129C
>>>>U3	343
>>>>U4	356
>>>>U5	270
>>>>>U5a	192 270
>>>>>>U5a1	192 256 270
>>>>>>>U5a1a	256 270 *399*
>>>>>U5b	189 270
>>>>>>U5b1	144 189 270
>>>>U6	172 219
>>>>>U6a	172 219 278
>>>>>>U6a1	172 189 219 278
>>>>>U6b	172 219 311
>>>>U7	318T
>>>>K	224 311
>>>pre-HV	CRS
>>>>pre-HV (see note below)	126 362
>>>>HV	CRS
>>>>>HV1	*067*
>>>>>H	CRS
>>>>>V	298





Poreklo haploskupin

- Evropa: H, T, U, V, X, K, N, I, J
- Pod-Saharska Afrika: L, L1, L2, L3, L3*
- Azija: A, B, C, D, E, F, G (*C, D, E, in G pripadajo večji haploskupini M*)
- Ameriški domorodci: A, B, C, D, in X

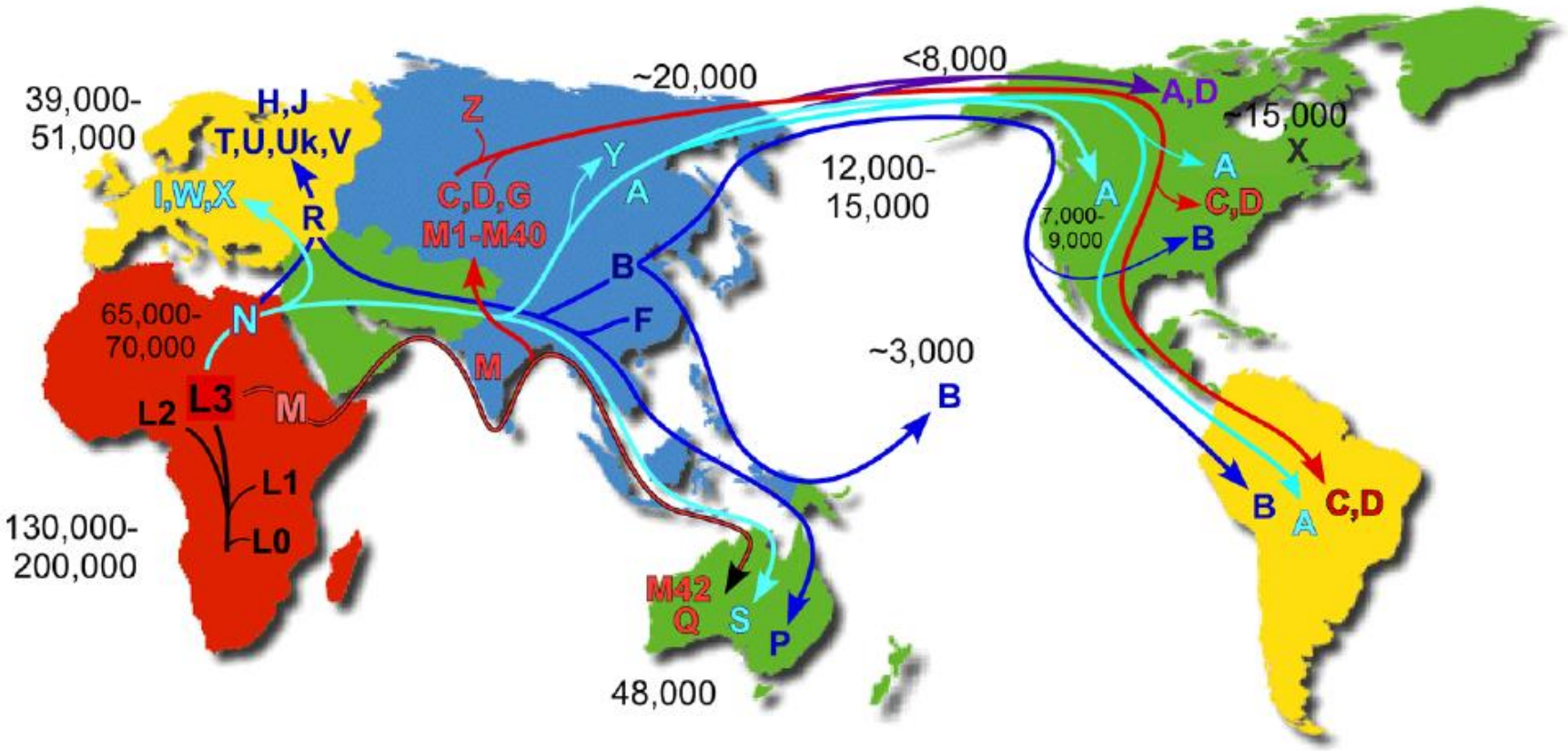


AL	Altaians	KO	Komi
AT	Aboriginal Taiwanese	KU	Kurds
		MA	Mansi
AU	Aleuts	MO	Mongols
AM	Amerinds	ND	Na-Dene
BU	Buryats	NI	Nivkhs
CH	Chukchi	PA	Palestine+Egypt
ES	Eskimo	PE	Persians (Iran)
EV	Evenks	PO	Polynesians
HA	Han Chinese	SA	Saami
HT	Han Taiwanese	SB	Sabah (Borneo)
HZ	Hazara	SP	South Pakistan
IN	India	TH	Thailand
IT	Itelmen	TU	Turks
JP	Japanese	UZ	Uzbeks
KE	Kets	YA	Yakuts

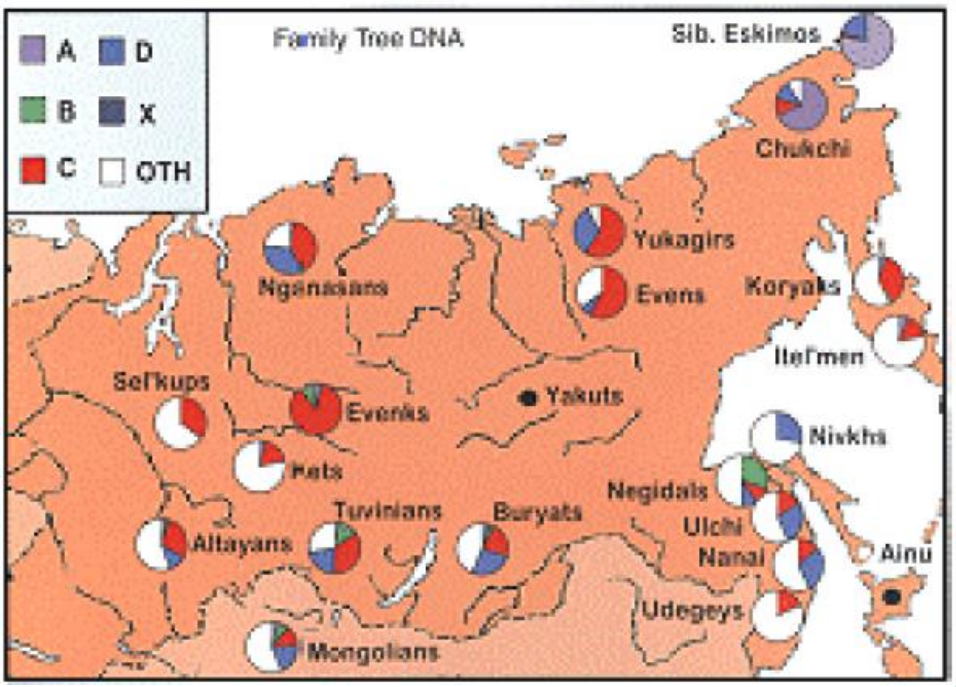
Specific tribes or locations are shown at left. Unlabelled pies are for general population in the area. African, American, and especially Polynesian areas are very large. The data in this chart is supposed to represent the situation before the recent European expansion beginning about 1500 AD. Assignments in Australia are somewhat iffy.

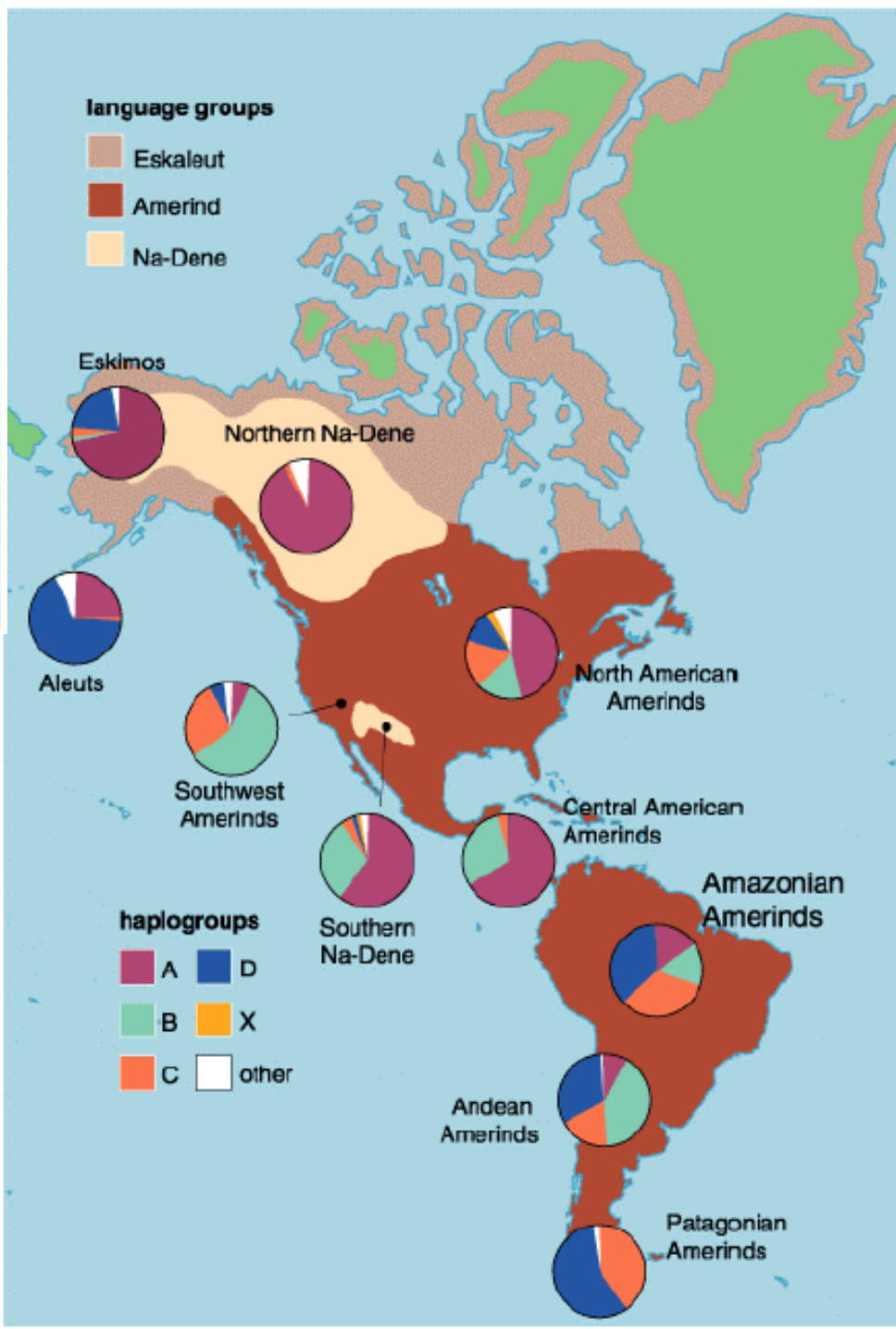
Human mtDNA Migrations

from http://www.mitomap.org



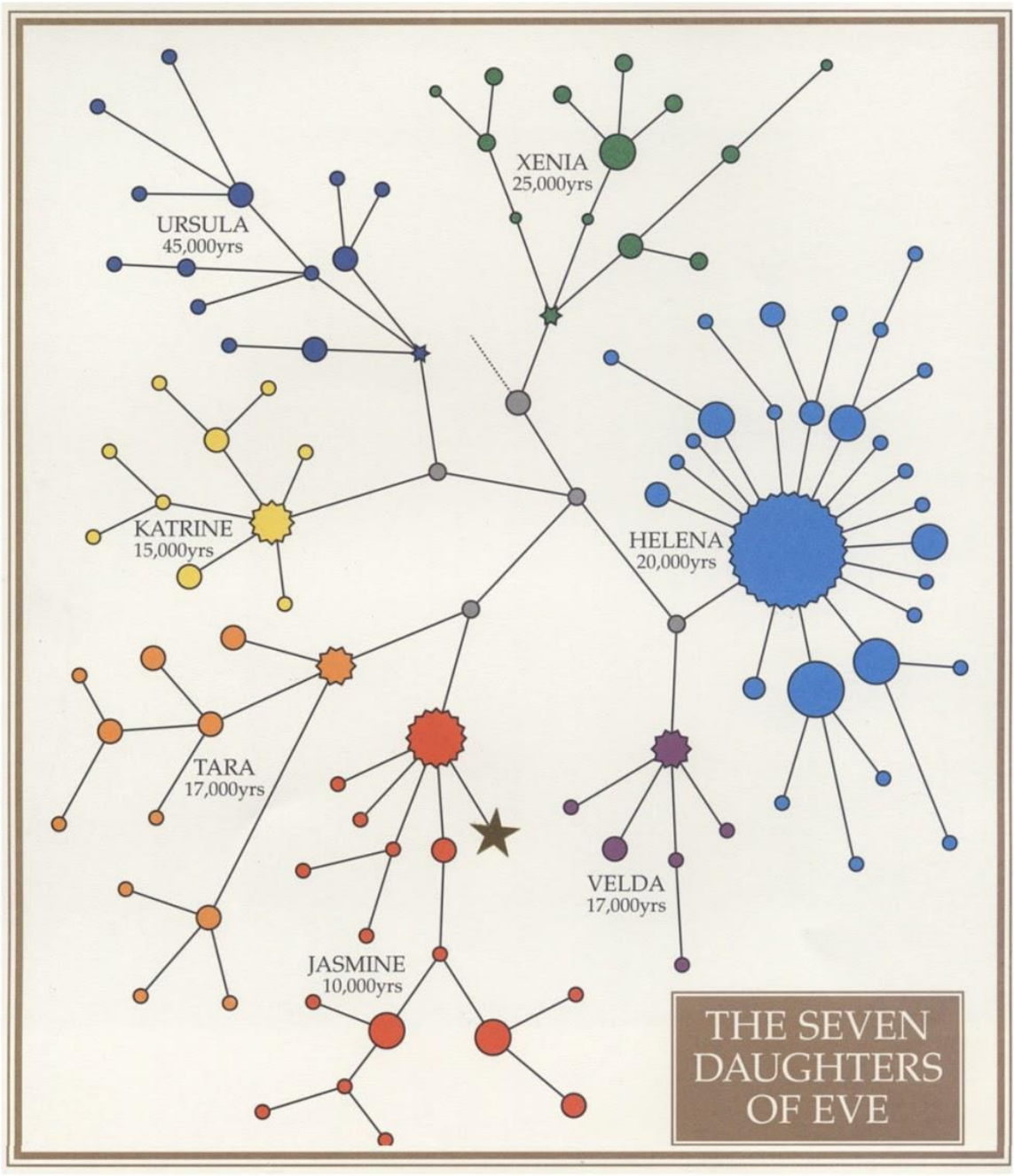
Mutation rate = 2.2 – 2.9% / MYR
Time estimates are YBP


A
D
B
X
C
OTH
Family Tree DNA
Sib. Eskimos
Chukchi
Yukagirs
Evens
Koryaks
Nganasans
Itel'men
Sel'kups
Evenks
Yakuts
Nivkhs
Negidals
Kets
Tuvinians
Buryats
Ulchi
Nanai
Altayans
Ainu
Udegeys
Mongolians


language groups
Eskaleut
Amerind
Na-Dene
Eskimos
Northern Na-Dene
Aleuts
North American Amerinds
Southwest Amerinds
Central American Amerinds
Amazonian Amerinds
Southern Na-Dene
haplogroups
A
D
B
X
C
other
Andean Amerinds
Patagonian Amerinds

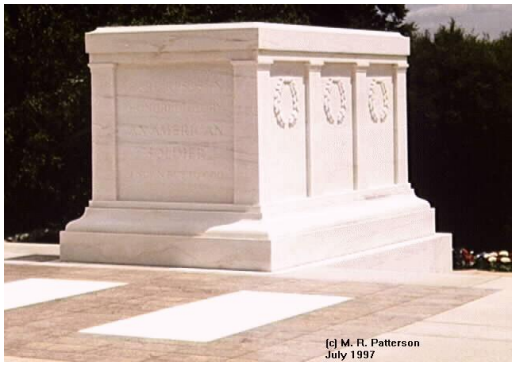
Mitohondrijska Eva

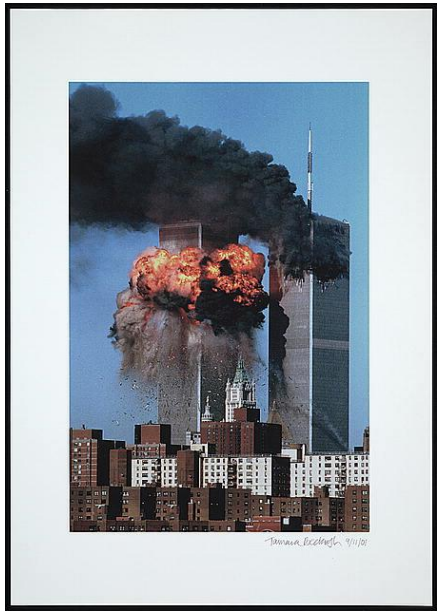
- Najstarejše ženske, ki so vir mtDNA določene skupine.



Velike nesreče in mtDNA

- Množična grobišča v Bosni
- 11/9
- Letalske nesreče
- Naravne nesreče (npr. tsunami)
- Zgodovinske preiskave

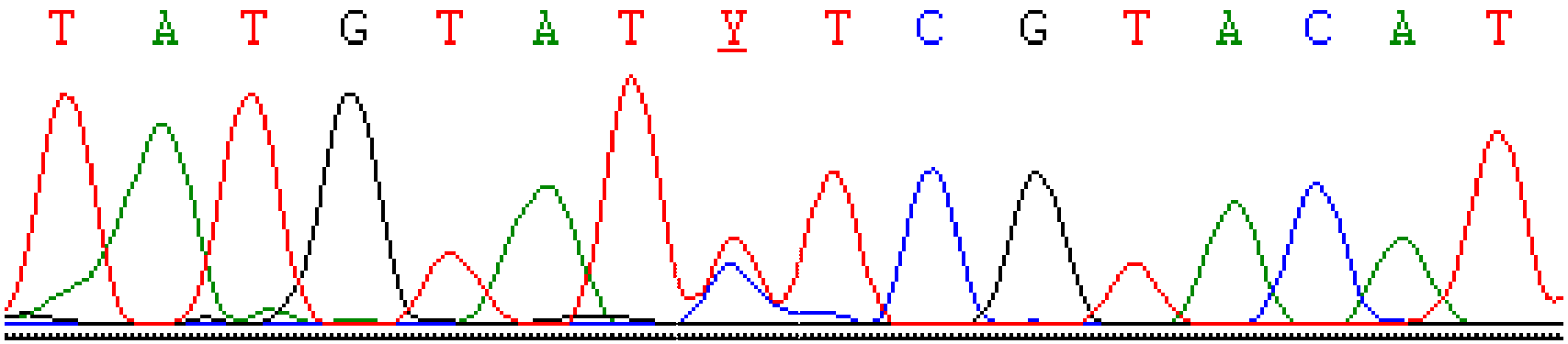


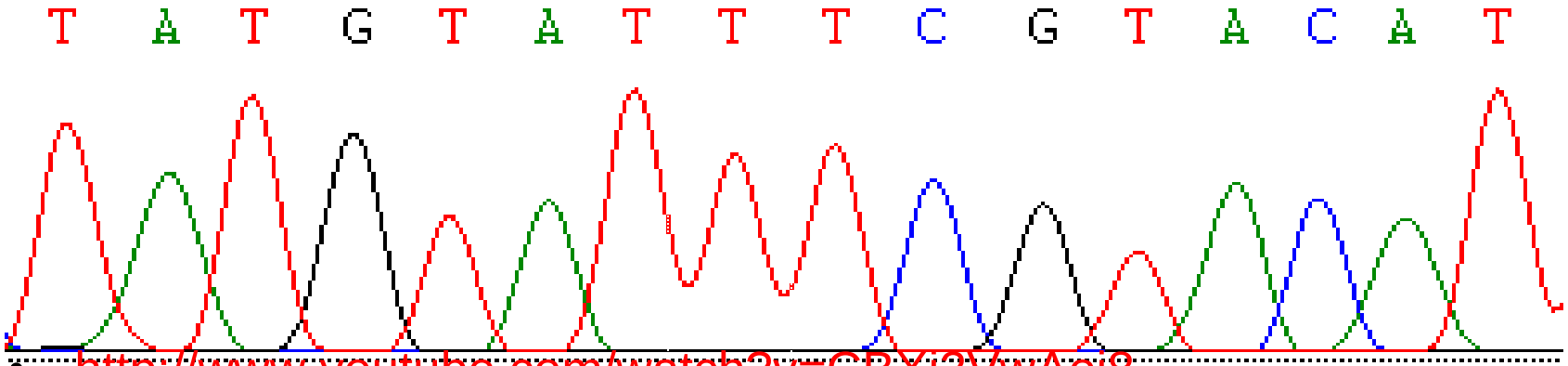


Družina Romanov

- Vladarji Rusije vse do 1916.
- Družino so ubili leta 1918 s streljanjem.
- Skupni grob je bil odkrit leta 1991. Najdeni so ostanki 4 moških in 5 žensk. Vendar je bilo ubitih 6 žensk.
- Poljakinja Anna Anderson je trdila, da je Anastasia.

Anastasia in Anna Anderson





- http://www.youtube.com/watch?v=CBXi2VwAoj8

- http://www.youtube.com/watch?v=CBXi2VwAoj8

Genomic identification in the historical case of the Nicholas II royal family

Evgeny I. Rogaev[a,b,c,d,1], Anastasia P. Grigorenko[b,d], Yuri K. Moliaka[b], Gulnaz Faskhutdinova[b], Andrey Goltsov[d], Arlene Lahti[e], Curtis Hildebrandt[e], Ellen L. W. Kittler[f], and Irina Morozova[a]

[a]Department of Genomics and Laboratory of Evolutionary Genomics, Vavilov Institute of General Genetics, Russian Academy of Science, Gubkina Street, 3, Moscow, 119991, Russian Federation; [b]Brudnick Neuropsychiatric Research Institute, University of Massachusetts Medical School, 303 Belmont Street, Worcester, MA 01604; [c]Faculty of Bioinformatics and Bioengineering, Lomonosov Moscow State University, Moscow, 119991, Russian Federation; [d]Research Center of Mental Health, Russian Academy of Medical Science, Zagorodnoe Shosse 2/2, Moscow, 113152, Russia; [e]Molecular World, Inc., Thunder Bay, ON, Canada P7B 2T1; and [f]University of Massachusetts Medical School, Center for AIDS Research, Worcester, MA 01605

Communicated by James D. Watson, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, November 14, 2008 (received for review October 8, 2008)

Accurate unambiguous identification of ancient or historical specimens can potentially be achieved by DNA analysis. The controversy surrounding the fate of the last Russian Emperor, Nicholas II, and his family has persisted, in part, because the bodies of 2 children, Prince Alexei and 1 of his sisters, have not been found. A grave discovered in 1991 contained remains putatively identified as those of the Russian Royal family. However, not all family members were represented. Here, we report the results of genomic analyses of new specimens, the human remains of 2 burned skeletons exhumed from a grave discovered in July 2007, and the results of a comprehensive genomic analysis of remains from the 1991 discovery. Additionally, ≈117 years old archival blood specimens from Nicholas II were obtained and genotyped, which provided critical material for the specific determination of individual identities and kinship identifications. Results of genotypic analyses of damaged historical specimens were evaluated alongside samples from descendants of both paternal and maternal lineages of the European Royal families, and the results conclusively demonstrate that the recently found remains belong to children of Nicholas II: Prince Alexei and his sister. The results of our studies provide unequivocal evidence that the remains of Nicholas II and his entire family, including all 5 children, have been identified. We demonstrate that convergent analysis of complete mitochondrial genome sequences combined with nuclear DNA profiles is an efficient and conclusive method for individual and kinship identification of specimens obtained from old historic relics.

fragments were badly damaged by fire and presumably by sulfuric acid. Preliminary anthropological examinations of the semiburned bone fragments excavated from the shallow pit suggest that they are from a boy who was approximately between 10 and 14 years of age and of a young woman who was approximately between 18 and 23 years of age at the time of their deaths. We demonstrate here that convergent analysis of complete mt genome sequences coupled with nuclear (especially Y chromosome) profiles can be efficiently applied to historical relics for complex human kinship and individual identification.

Results and Discussion

For genetic analysis we selected 3 relatively well-preserved bone specimens (N141, N146, and N147) from the second grave. The bone samples from the putative skeletal remains of Nicholas II (N4), his wife Alexandra (N7) and 3 of their daughters (N3, N5, N6) from the first grave were also available. DNA was extracted from these specimens for this study. The maternal reference samples were collected from descendants of 2 maternal lineages, Queen Victoria (1819–1901) and Empress Maria Feodorovna (1847–1928) (known also as Princess Dagmar, daughter of Louise of Hesse-Cassel and Christian IX, King of Denmark). The paternal reference samples were obtained from male lineage descendants of Emperor Nicholas I (1796–1855) (*SI Materials and Methods, Reference Samples*). Because de novo mutations may theoretically occur in subjects

Podatkovne baze

MITOMAP

MITOWEB
MITOMAP MITOMASTER MITOWIKI

Search

MITOMAP

- Log In
- Register
- Reset Password

MITOMAP
MITOMASTER
MITOWIKI

Tools
Help
Search
Feedback
Index

MITOMAP
A human mitochondrial genome database

A compendium of polymorphisms and mutations in human mitochondrial DNA

MITOMAP reports published and unpublished data on human mitochondrial DNA variation. Most of the data is hand-curated and, due to the massive volume of sequencing data being produced world wide, there is always a backlog of papers and data to be added. If you would like to fast-track inclusion of a paper and its data into MITOMAP, please email a pdf to mitomap@email.chop.edu. We appreciate your help. Thanks.

MITOMAP Quick Reference

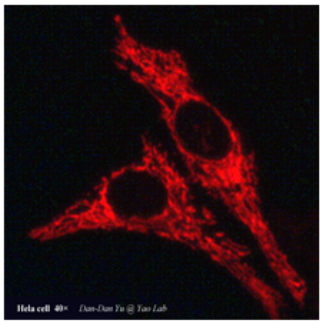
- **To search for point mutations, click here**. The info button on the search page has more information.
- The rCRS is GenBank number **NC_012920**. Click here for details.

General References	Illustrations:
The Annotated Human Mitochondrial DNA Sequence	View Figures
The rCRS & other mtDNAs	-Mitochondrial DNA Map
Amino Acid Translation Tables	-Eleven pathological mutations in tRNA
Mitochondrial References, ALL (very large file) • A-L only • M-Z only	-Mitochondrial energetics
Haplogroup Markers & Frequencies Simpler mtDNA Tree: Europe, Asia, Africa	-Diabetes metabolism & the mitochondria
Mitochondrial DNA Function Locations (Gene Loci)	-World migrations
Mitochondrial DNA Polypeptide Assignments	-mtDNA Trees
Complete Mitochondrial Genome Sequences	
Archived Reports:	
Mitochondrial Human Genome Report	**Other databases & tools:**
Common Continent-Specific mtDNA Variants, c.1995	PhyloTree mtDB HaploGrep
mtDNA RFLPs: High Resolution Low Resolution	MitoTool MitoWheel HvrBase
	mtDNA Manager mitoLSDB mtSNP
mtDNA Variants (includes mini insertions & deletions)	Mammalian Mitochondrial tRNA Genes
UPDATED Control Region Variants (16024-576)	HmtDB database MitoMiner
UPDATED Coding & RNA Variants (577-16023, MTTF-MTTP)	EMPOP CR Database mtTree.ru
Somatic Mutations	POLG Database
Collection of Unpublished Variants	Other Useful Mito Links on the Web
mtDNA Mutations with Reports of Disease-Associations	
Organized by mtDNA location:	

MitoTool

MitoTool mtDNA tree Build 14

Home | Use rCRS | Use RSRS | Database | Statistics | Manual | About Us



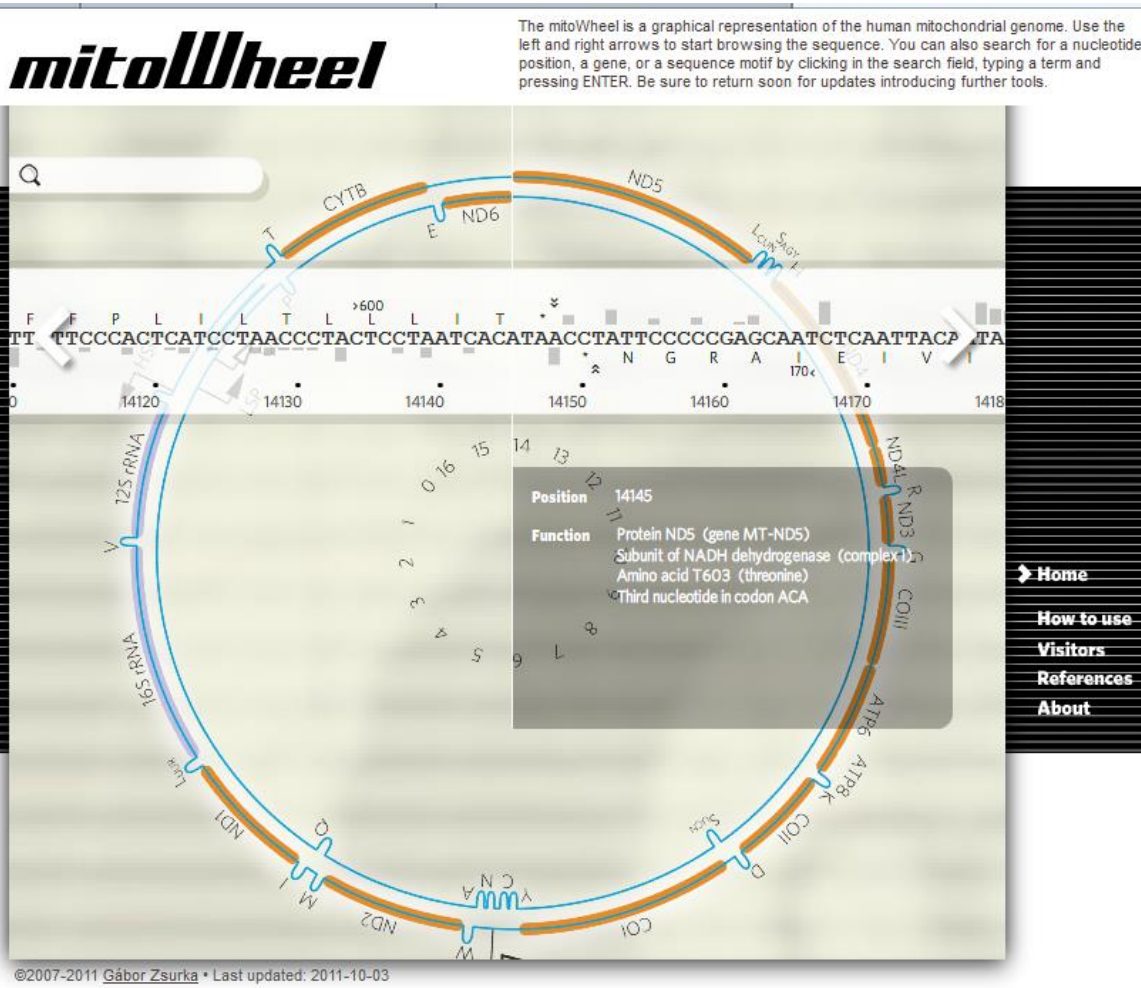
MitoTool, a web-based bioinformatics platform, provides a convenient, user-friendly interface for handling human mtDNA sequence data. It contains multiple modules which cover a wide array of functions: (i) to automatically yield a list of the variants in certain mtDNA relative to the revised Cambridge Reference Sequence (rCRS) recommended or the Reconstructed Sapiens Reference Sequence (RSRS) and determine the haplogroup status of that lineage according to Phylotree (www.phylotree.org), (ii) to detect missing sequence variants in certain mtDNA with claimed haplogroup status, (iii) to display the location of the variant, interspecies conservation index and change of amino acid status, (iv) to identify potentially pathogenic mutations based on the reported data, (v) to conduct statistical analysis for haplogroup distribution frequency between case and control groups, and (vi) to retrieve and batch download analytical output and mitochondrion-related data of interest. It is unique in its ability to recognize four types of mtDNA data, to process data in batch mode and to allow access without login requirement. We hope that this tool is helpful for mtDNA studies including molecular anthropology, population genetics, forensics and biomedical research.

Update News»

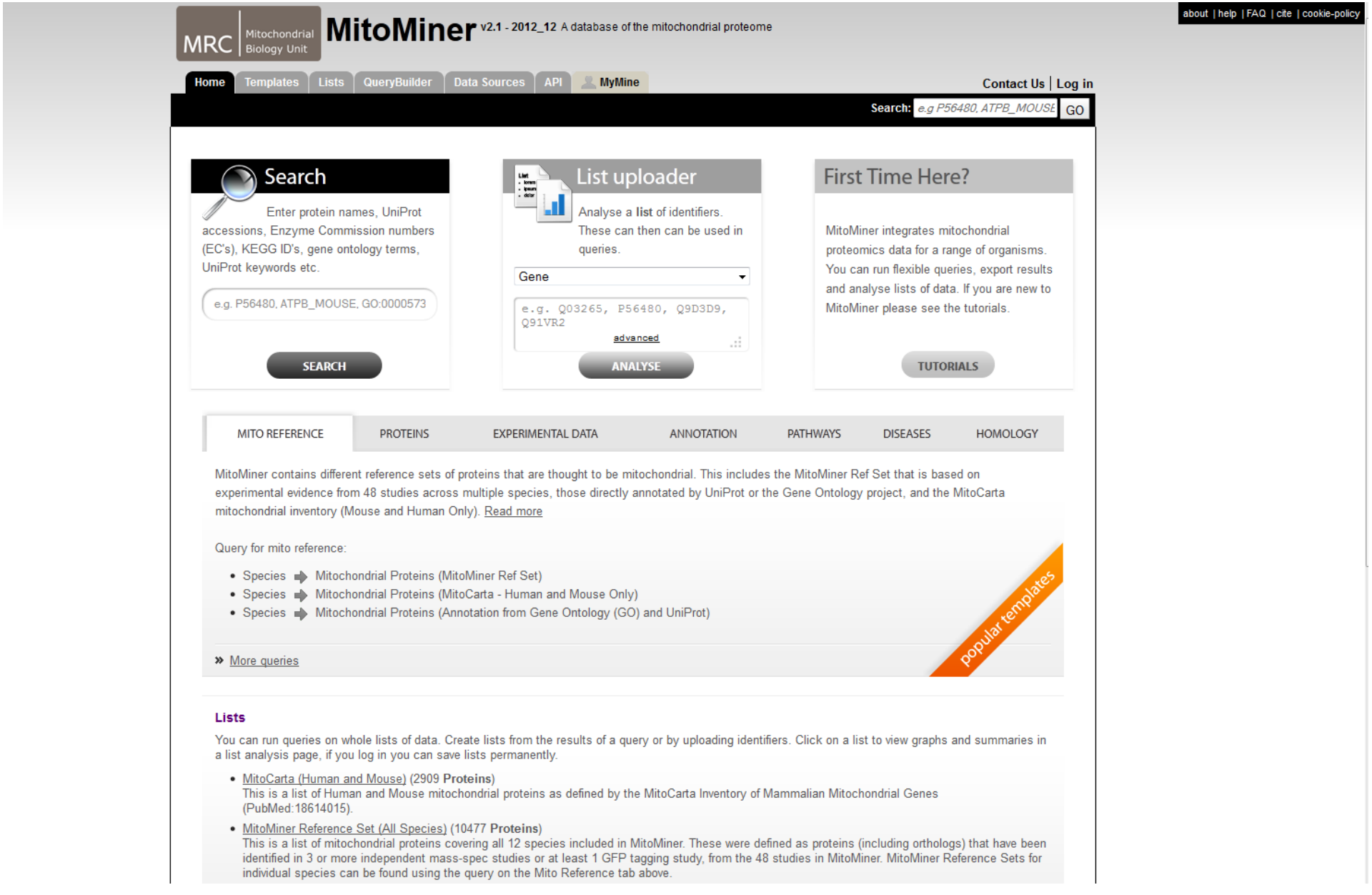
Download MitoTool Stand-alone Version

MitoTool Mirror Updated with mtDNA Tree Build 15

mitoWheel


mitoWheel
The mitoWheel is a graphical representation of the human mitochondrial genome. Use the left and right arrows to start browsing the sequence. You can also search for a nucleotide position, a gene, or a sequence motif by clicking in the search field, typing a term and pressing ENTER. Be sure to return soon for updates introducing further tools.
CYTB
ND6
ND5
14120
14130
14140
14150
14160
14170
12S rRNA
16S rRNA
ND1
ND2
COI
COII
ATP8
ATP6
ND3
ND4
Position 14145
Function Protein ND5 (gene MT-ND5)
Subunit of NADH dehydrogenase (complex I)
Amino acid T603 (threonine)
Third nucleotide in codon ACA
Home
How to use
Visitors
References
About
©2007-2011 Gábor Zsurka • Last updated: 2011-10-03

MitoMiner


about | help | FAQ | cite | cookie-policy
MRC Mitochondrial Biology Unit
MitoMiner v2.1 - 2012_12 A database of the mitochondrial proteome
Home
Templates
Lists
QueryBuilder
Data Sources
API
MyMine
Contact Us | Log in
Search: e.g P56480, ATPB_MOUSE
GO
Search
Enter protein names, UniProt accessions, Enzyme Commission numbers (EC's), KEGG ID's, gene ontology terms, UniProt keywords etc.
e.g. P56480, ATPB_MOUSE, GO:0000573
SEARCH
List uploader
Analyse a list of identifiers. These can then can be used in queries.
Gene
e.g. Q03265, P56480, Q9D3D9, Q91VR2
advanced
ANALYSE
First Time Here?
MitoMiner integrates mitochondrial proteomics data for a range of organisms. You can run flexible queries, export results and analyse lists of data. If you are new to MitoMiner please see the tutorials.
TUTORIALS
MITO REFERENCE
PROTEINS
EXPERIMENTAL DATA
ANNOTATION
PATHWAYS
DISEASES
HOMOLOGY
MitoMiner contains different reference sets of proteins that are thought to be mitochondrial. This includes the MitoMiner Ref Set that is based on experimental evidence from 48 studies across multiple species, those directly annotated by UniProt or the Gene Ontology project, and the MitoCarta mitochondrial inventory (Mouse and Human Only). Read more
Query for mito reference:
Species Mitochondrial Proteins (MitoMiner Ref Set)
Species Mitochondrial Proteins (MitoCarta - Human and Mouse Only)
Species Mitochondrial Proteins (Annotation from Gene Ontology (GO) and UniProt)
popular templates
More queries
Lists
You can run queries on whole lists of data. Create lists from the results of a query or by uploading identifiers. Click on a list to view graphs and summaries in a list analysis page, if you log in you can save lists permanently.
MitoCarta (Human and Mouse) (2909 Proteins)
This is a list of Human and Mouse mitochondrial proteins as defined by the MitoCarta Inventory of Mammalian Mitochondrial Genes (PubMed:18614015).
MitoMiner Reference Set (All Species) (10477 Proteins)
This is a list of mitochondrial proteins covering all 12 species included in MitoMiner. These were defined as proteins (including orthologs) that have been identified in 3 or more independent mass-spec studies or at least 1 GFP tagging study, from the 48 studies in MitoMiner. MitoMiner Reference Sets for individual species can be found using the query on the Mito Reference tab above.

PhyloTree

PhyloTree.org

Please cite the mtDNA tree as follows:

van Oven M, Kayser M. 2009. Updated comprehensive phylogenetic tree of global human mitochondrial DNA variation. Hum Mutat 30(2):E386-E394. http://www.phylotree.org.
doi:10.1002/humu.20921

Here we provide a phylogenetic tree of global human mitochondrial DNA variation, based on both coding- and control-region mutations, and including haplogroup nomenclature. This mtDNA tree is meant as a framework for evolutionary anthropologists, medical geneticists, genealogists and forensic geneticists. The tree will be updated at least every six months (unless no new data has appeared).

mtDNA tree Build 15 (30 Sep 2012)

What is new?
rCRS-oriented version of Build 15
Previous Builds of the mtDNA tree
Database of 16810 entire human mtDNA sequences (updated 30 Sep 2012)

Additional resources

The Reconstructed Sapiens Reference Sequence (RSRS), annotated
The revised Cambridge Reference Sequence (rCRS), annotated
Summary of the differences between RSRS and rCRS
Genomic organization of human mtDNA, linearized view
MtDNA sequences of human's closest relatives

Maintained by Mannis van Oven (m.vanoven @ erasmusmc.nl)
Department of Forensic Molecular Biology
Erasmus MC, University Medical Center Rotterdam
The Netherlands

Bolezni

Vzroki za mitohondrijske bolezni

- Dedovanje DNA iz jedra
- Dedovanje MtDNA
- Kombinacija napak v mtDNA ter nDNA
- Naključne napake v DNA

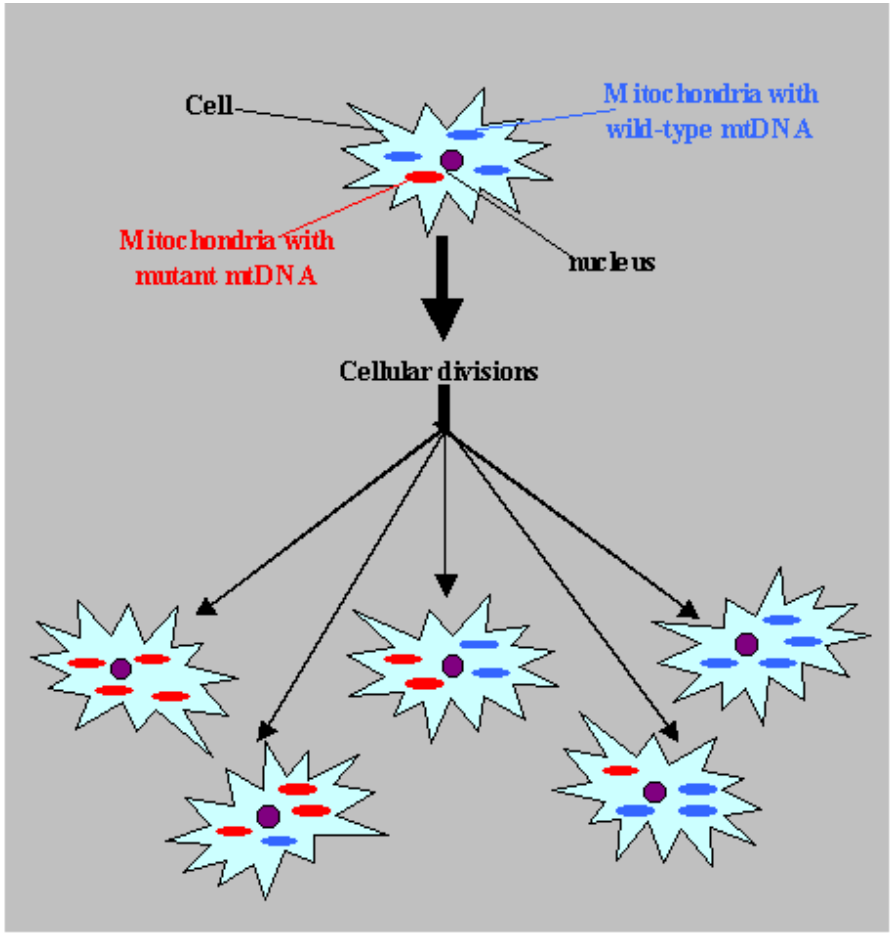
Simptomi nenormalnih mitohondrijev

Tip mitohondrijske bolezni je opredeljena glede na simptome ter prizadetega organa.

- Slaba rast
- Izguba mišične koordinacije, šibke mišice
- Bolezni srca, jeter ali ledvic
- Gastrointestinalne bolezni, hudo zaprtje
- Bolezni dihal
- Bolezni tiroidne žleze
- Diabetes
- Povečena nevarnost okužbe
- Problemi z vidom in sluhom
- Nevrološki problemi, epileptični napadi
- Demenca
- Zastoji v razvoju, težave z učenjem, mentalna zaostalost

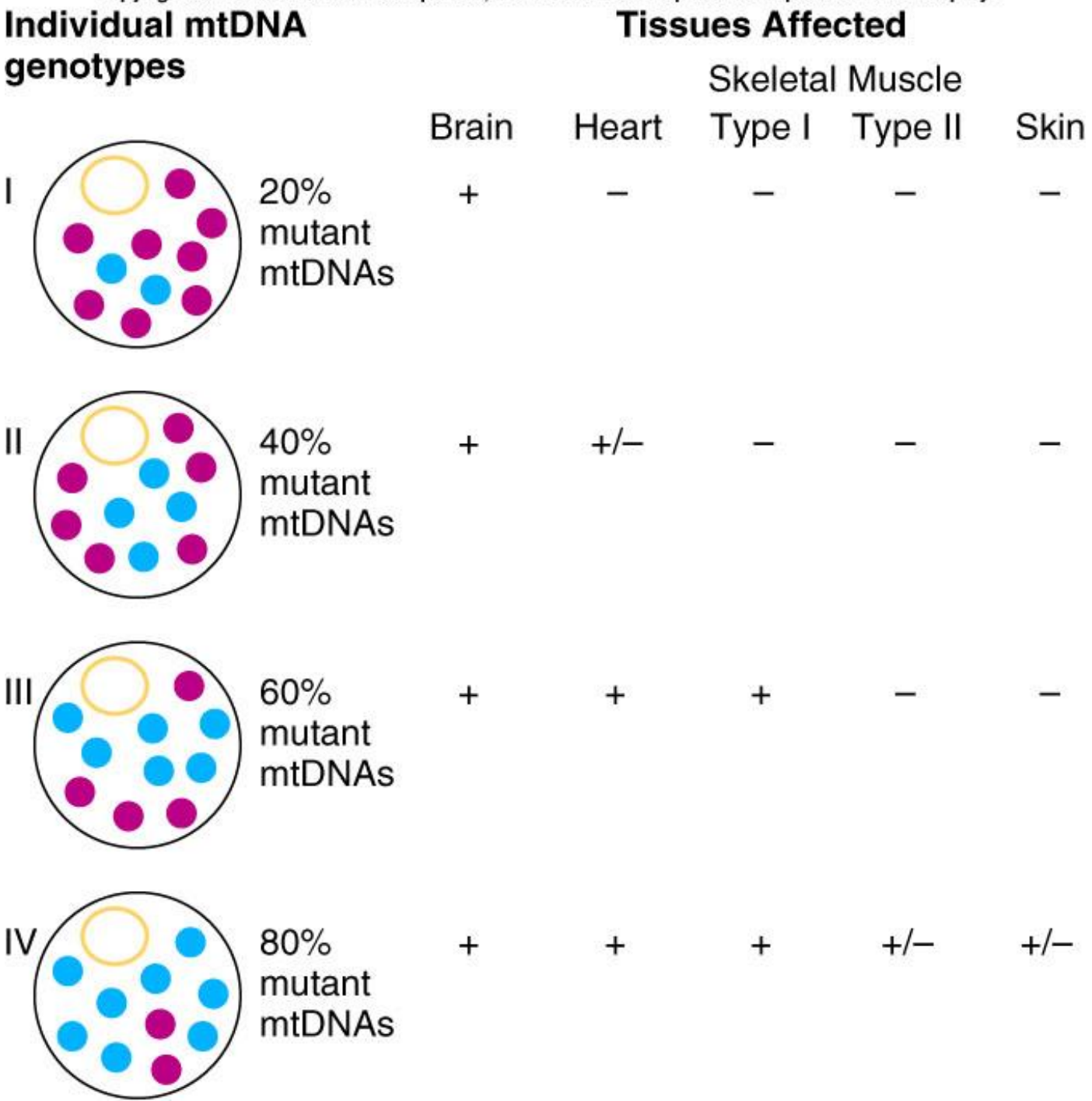
Heteroplazmija

- Hetroplazmija – osebek ima več kot en tip mitohondrijev
- Homoplazmija – samo en tip mit.
- Ob delitvi celic se mitohondriji delijo naključno. Različe celice dobijo različne deleže tipov mit.
- Če je en tip mit normalen drugi pa mutiran, je jakost simptomov v različnih tkivih odvisna tudi od delža obeh tipov.
- Naključna razdelitev dveh tipov med oogenezo lahko povzroči bolezen pri nekaterih potomcih, pri drugih pa ne.
- Heteroplazmija je lahko koristna – stoletniki kažejo nadpovprečno stopnjo heteroplazmije [Rose G, BMC GENOMICS 8: 293].

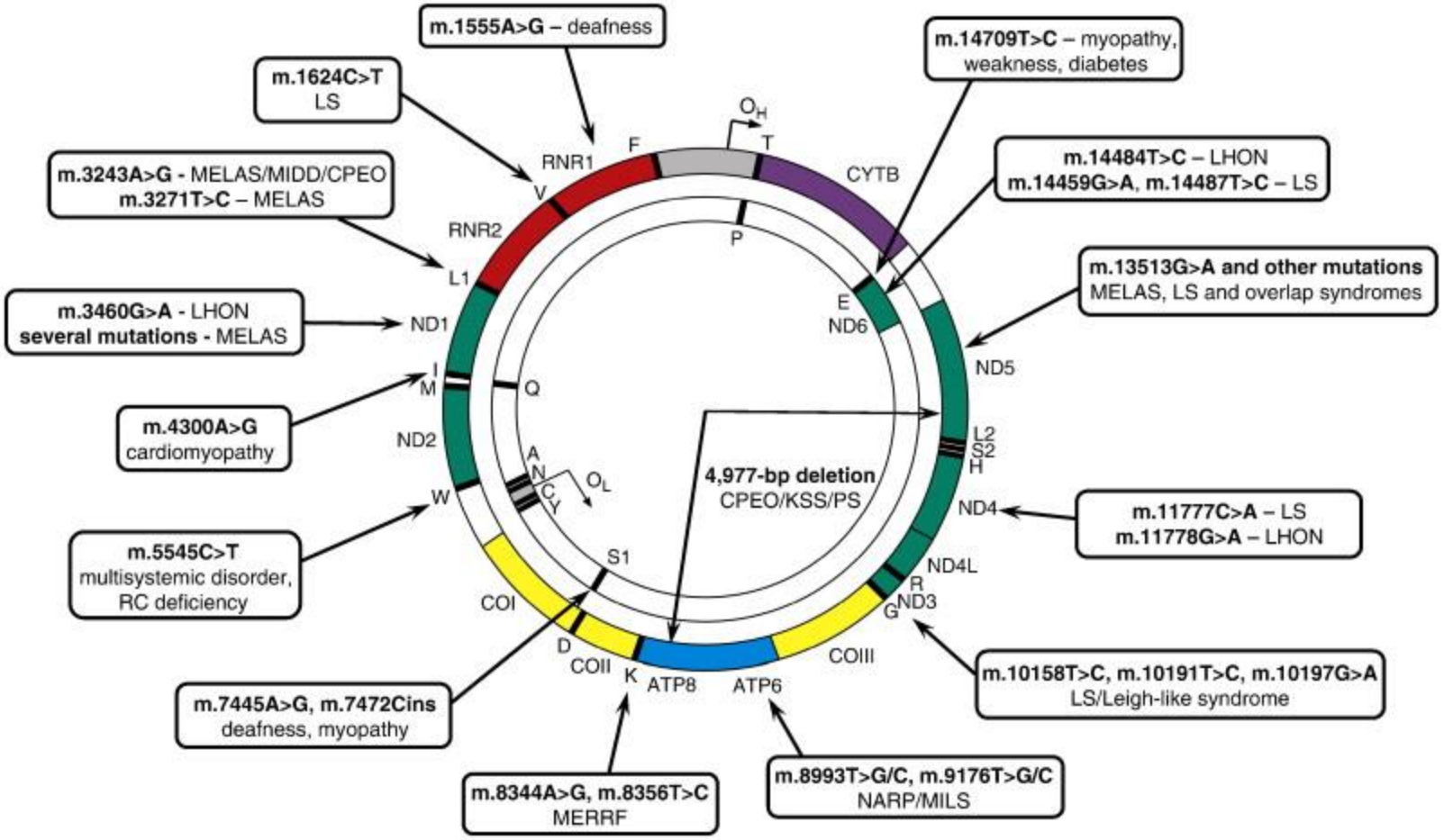


Resnost bolezni je odvisna od deleža mutiranih mitohondrijev.

Tkiva, ki rabijo več ATP so bolj občutljiva.



Mitohondrijske mutacije



http://dx.doi.org/10.1016/j.bbabio.2009.09.005

Genetske bolezni mitohondrijev

Table 16.1 Phenotypes associated with some mitochondrial mutations

Phenotypes

Nucleotide changed	Mitochondrial component affected	Phenotype[a]
3460	ND1 of Complex I[b]	LHON
11778	ND4 of Complex I	LHON
14484	ND6 of Complex I	LHON
8993	ATP6 of Complex V[b]	NARP
3243	$tRNA^{Leu(UUR)}$[c]	MELAS, PEO
3271	$tRNA^{Leu(UUR)}$	MELAS
3291	$tRNA^{Leu(UUR)}$	MELAS
3251	$tRNA^{Leu(UUR)}$	PEO
3256	$tRNA^{Leu(UUR)}$	PEO
5692	$tRNA^{Asn}$	PEO
5703	$tRNA^{Asn}$	PEO, myopathy
5814	$tRNA^{Cys}$	Encephalopathy
8344	$tRNA^{Lys}$	MERRF
8356	$tRNA^{Lys}$	MERRF
9997	$tRNA^{Gly}$	Cardiomyopathy
10006	$tRNA^{Gly}$	PEO
12246	$tRNA^{Ser(AGY)}$[c]	PEO
14709	$tRNA^{Glu}$	Myopathy
15923	$tRNA^{Thr}$	Fatal infantile multisystem disorder
15990	$tRNA^{Pro}$	Myopathy

[a] LHON Leber's hereditary optic neuropathy; NARP Neurogenic muscle weakness, ataxia, retinitis pigmentosa; MERRF Myoclonic epilepsy and ragged-red fiber syndrome; MELAS Mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes; PEO Progressive external ophthalmoplegia.

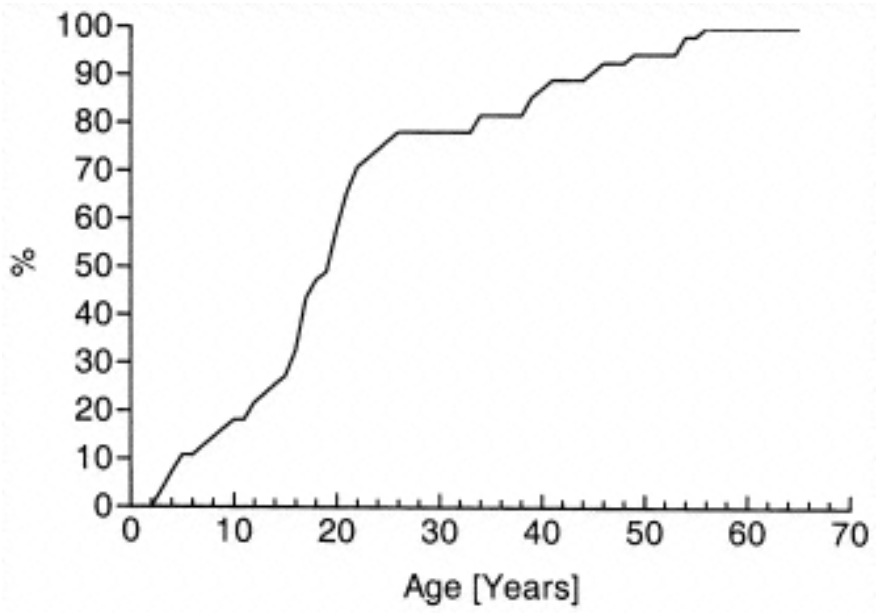
[b] Complex I is NADH dehydrogenase. Complex V is ATP synthase.

[c] In $tRNA^{Leu(UUR)}$, the R stands for either A or G; in $tRNA^{Ser(AGY)}$, the Y stands for either T or C.

Genetske bolezni mitohondrijev -LHON

Leberjeva dedna optična nevropatija

- Poimenovana po Theodore Leberju, ki jo je opisal leta 1871
- Progresivna izguba vida iz centra proti periferiji. Običajno se začne pri dvajsetih letih.
- Ponavadi se vid izgubi najprej na eno oko, nato kmalu na drugem očesu. Včasih istočasno.
- Največkrat se bolezen izrazi pri mladih moških (85%). Ne ve se, zakaj.
- Možnost prenosa na potomce je ~20% (heteroplasmija). Precej sporadičnih primerov.



- Prevalenca 1:50.000
- Večina primerov bolezni je zaradi mutacije Arg v His pri NADH dehidrogenazi. Znanih je 18 mutacij, ki so vse v kodirajočem delu proteinov respiratorne verige.
- Pride do odmiranja vlaken optičnih živcev.
- Drugi simptomi: srčna aritmija, nevrološke motnje, periferne nevropatije, nespecifične miopatije in motnje gibanja.

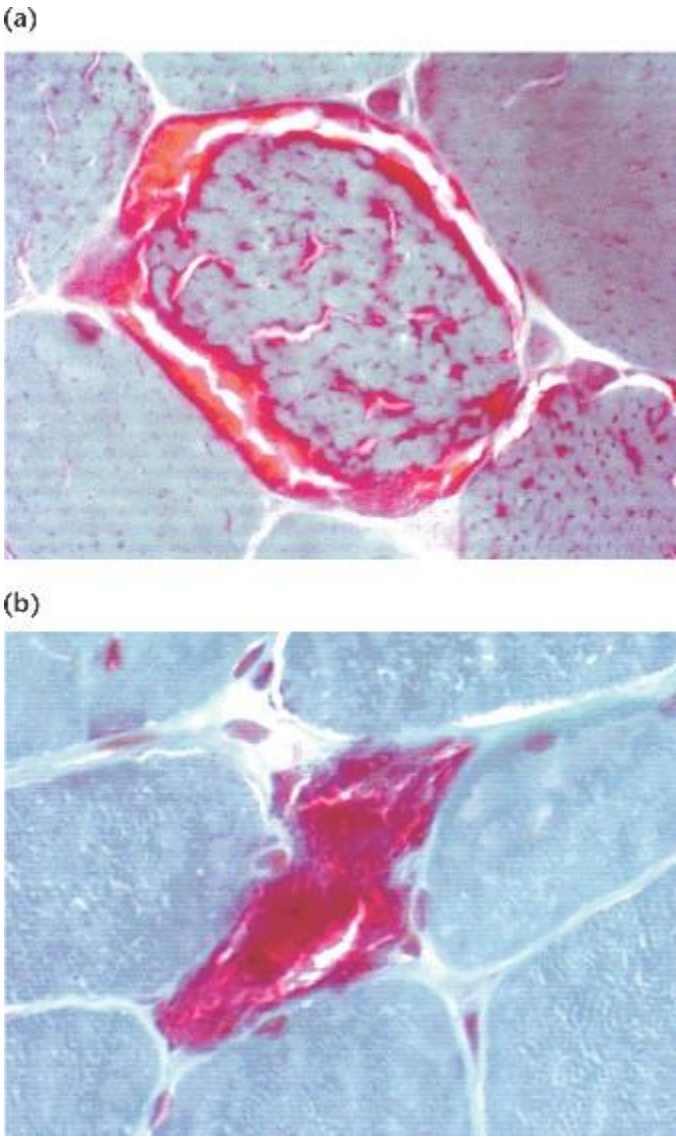
Zdravljenje LHON

- Ni dokazanega učinkovitega zdravljenja
- Boljše je preprečiti kot zdraviti
  - zmanjšanje kajenja in alkohola.
  - Lahko pomaga uravnana prehrana, bogata z antioksidanti (Vitamini A, C, in E, ter cink)
  - Uporabljajo se tudi prehrambeni dodatki (npr. Co-encim Q10)

MERRF – miokloničnа epilepsija in raztrganost rdečih vlaken

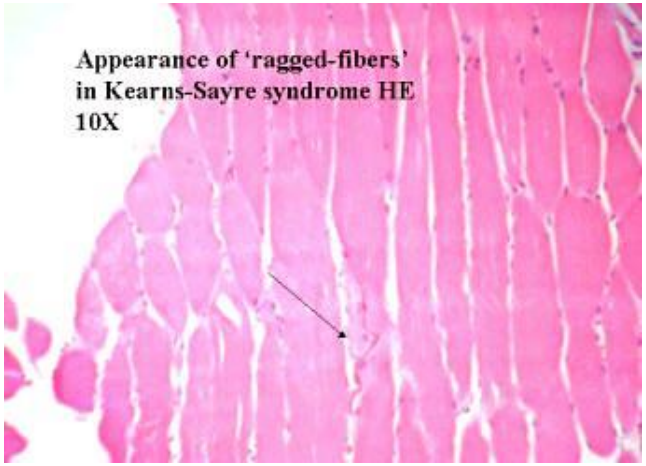
Myoclonic epilepsy and ragged red fiber disease (MERRF).

- Simptomi v CŽS: epilepsija, gluhost, demenca. Nenaravne skeletne in srčne mišice. Nenavadni mitohondriji.
- Napake pri več proteinih respiratorne verige.
- Večinoma zaradi mutacije A->G $tRNA^{lys}$ (mutacija A8344G).
- Enostavna diagnoza, ker se spremeni eno restrikcijsko mesto.
- Precej variacije pri dedovanju bolezni.
- Močna korelacija med % mutiranih mitohondrijev in resnostjo bolezni.



Kearns-Sayre sindrom

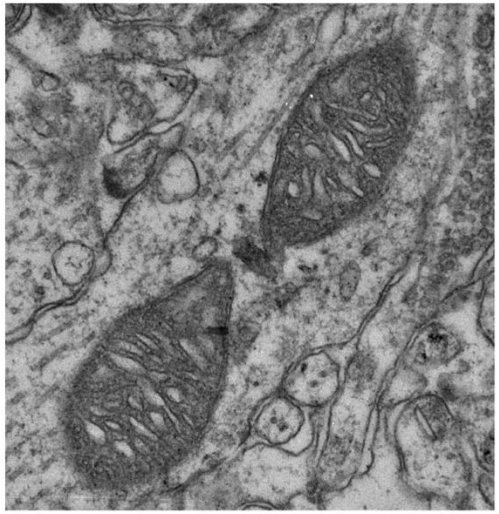
- Simptomi: Paraliza mišic, težave s srčno mišico, degeneracija mrežnice, epilepsije.
- Zaradi večjih delecij mtDNA. Obstaja več variant.
- Večinoma sporadično, redko dedno.
- Heteroplazmija je nujna za preživetje.



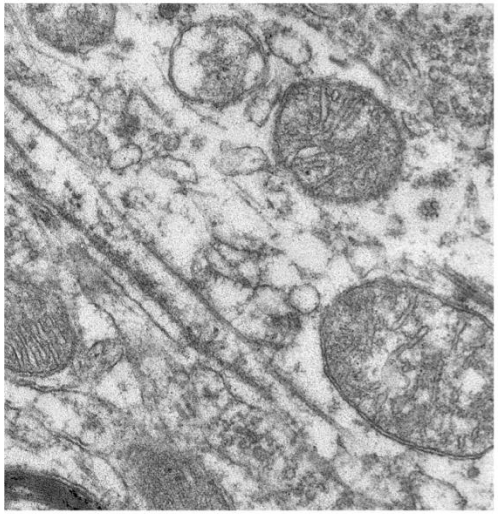
Mitohondriji in nevrodegenerativne bolezni

- Približno tretjina genov, katerih mutacije so povezane z nevrodegeneracijo, so pomembne za funkcionirnje mitohondrijev.
- Pri AD pride do opaznih sprememb v številu in morfologiji mitohondrijev.
- Inhibicija respiratornih kompleksov inducira nevrodegeneracijo v določenih delih možganov, ki imajo določene podobnosti s pravimi boleznimi.
  - Nevrotoksina rotenon in MPTP, ki vplivata na kompleks 1, uničujeta dopaminergične nevrone in povzročata simptome, podobne Parkinsonovi bolezni.
  - Inhibitor sukcinat dehidrogneaze 3- nitropropionska kislina sproži nevrodegeneracijo v striatumu in simulira Huntingtonovo bolezen.

Mitohondriji in staranje



Young



Old

1. Zmanjša se nivo kardiolipina in pride do strukturnih napak.
2. Zmanjša se membranski potencial (gonilna sila sinteze ATP) in celična poraba kisika.
3. Povečana oksidacija in heterogenost.
4. Nagnjenost k oksidativnim poškodbam.

Skeletne mišice in staranje