Mitochondria & Aging

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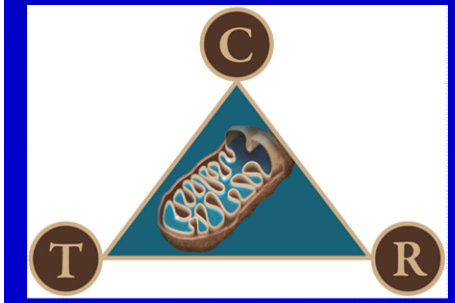
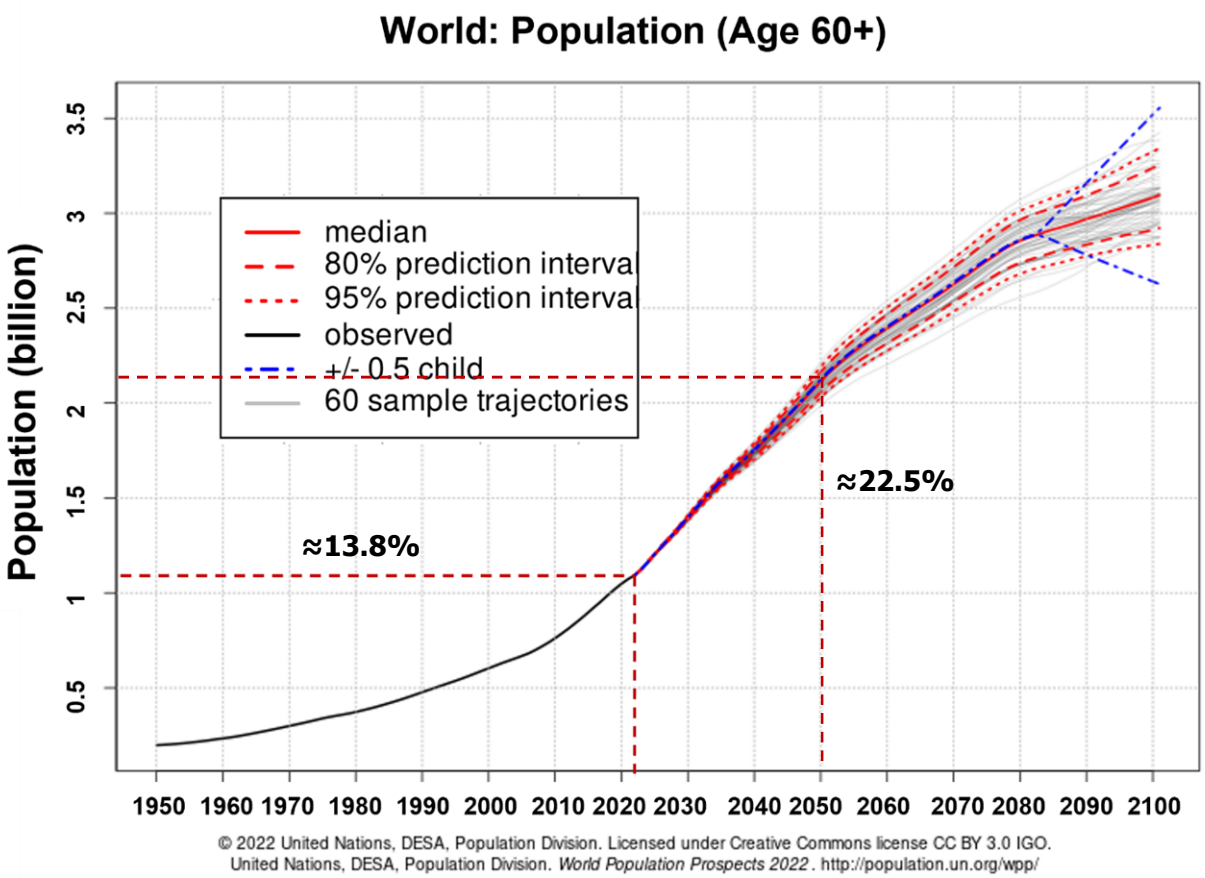
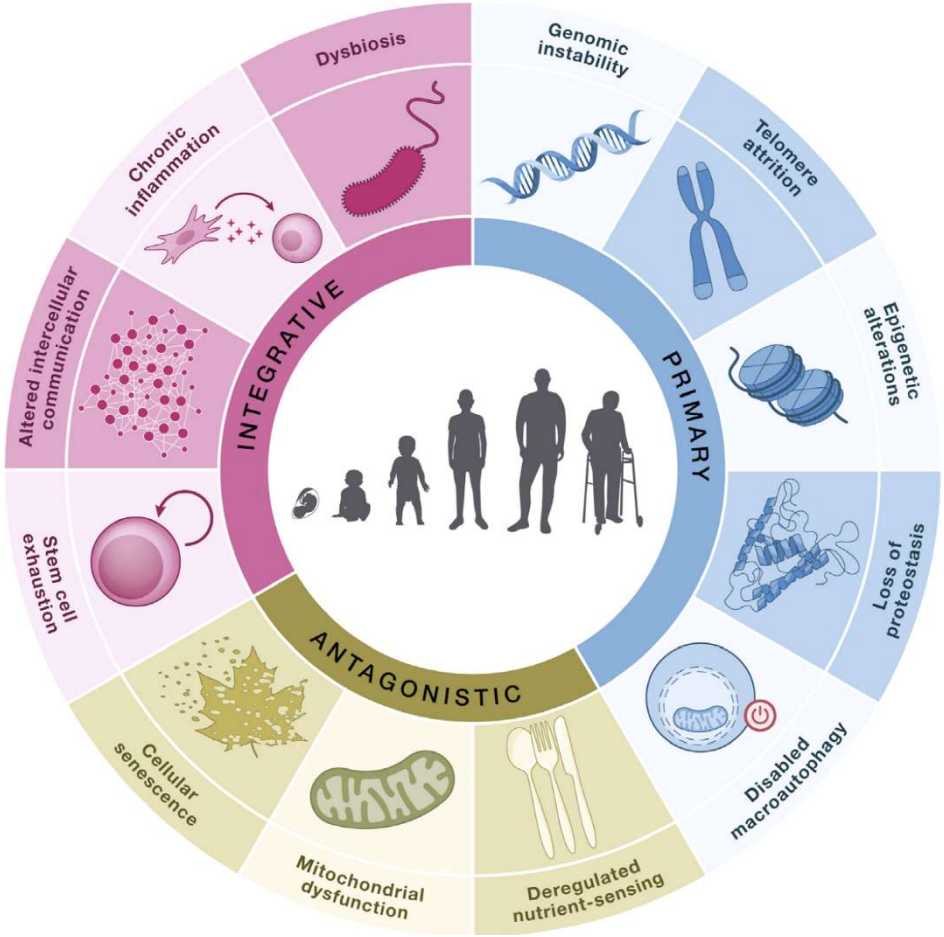


The World's Population is Aging Rapidly



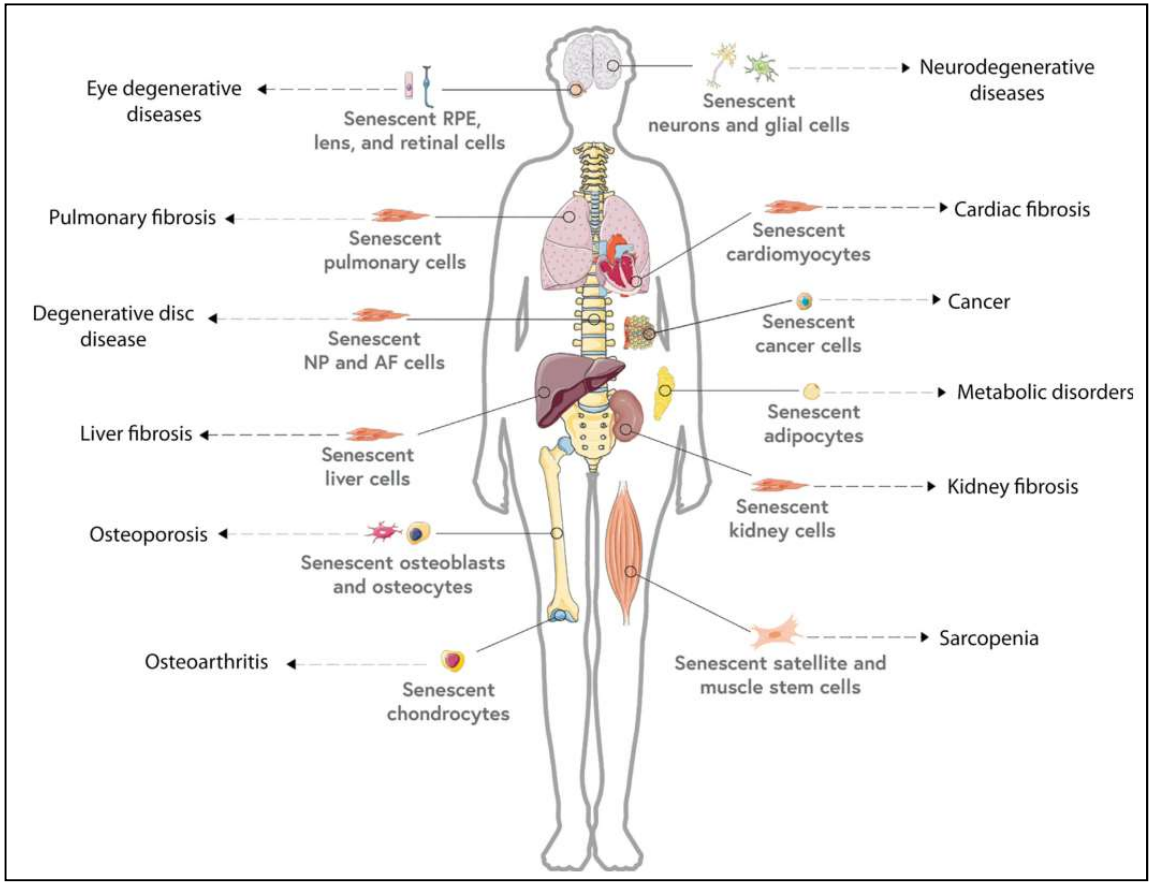
(United Nations, World Population Prospects 2022)

Hallmarks of Aging



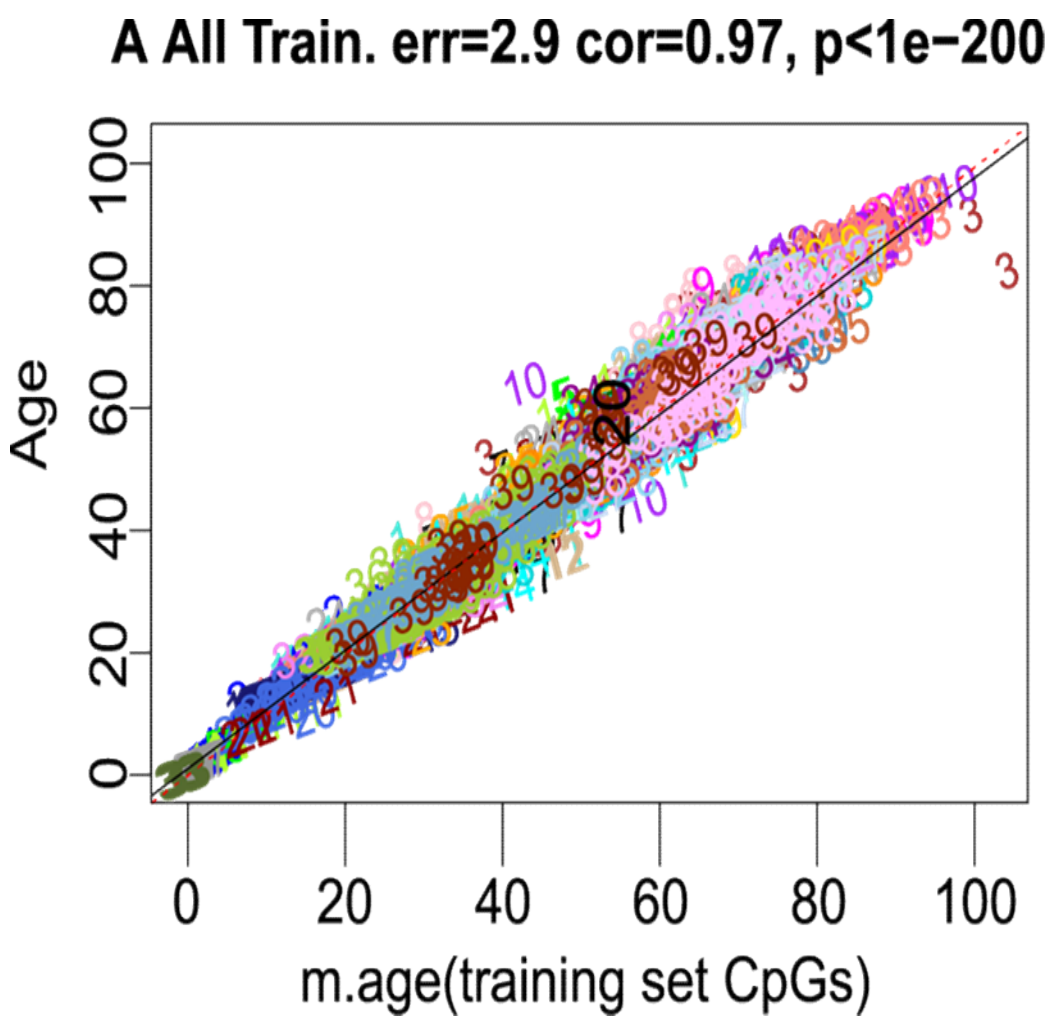
(*Cell*, 2023)

Senescent cells drive aging and diseases



M. Demaria, *et al*. Trends in Cell Biology, 2020.

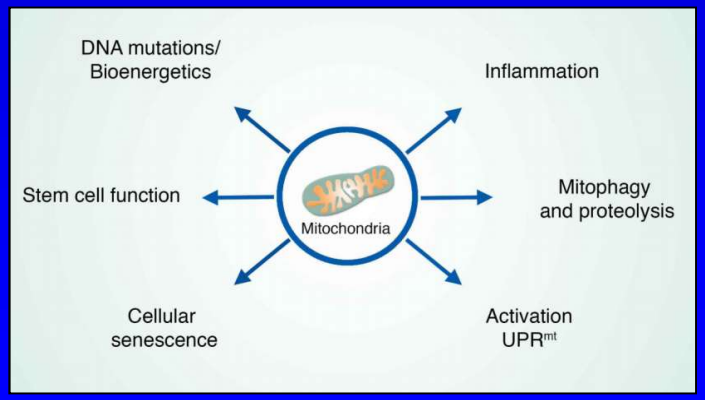
Breakthrough Works in Aging



Horvath et al

Major Mitochondrial Functions

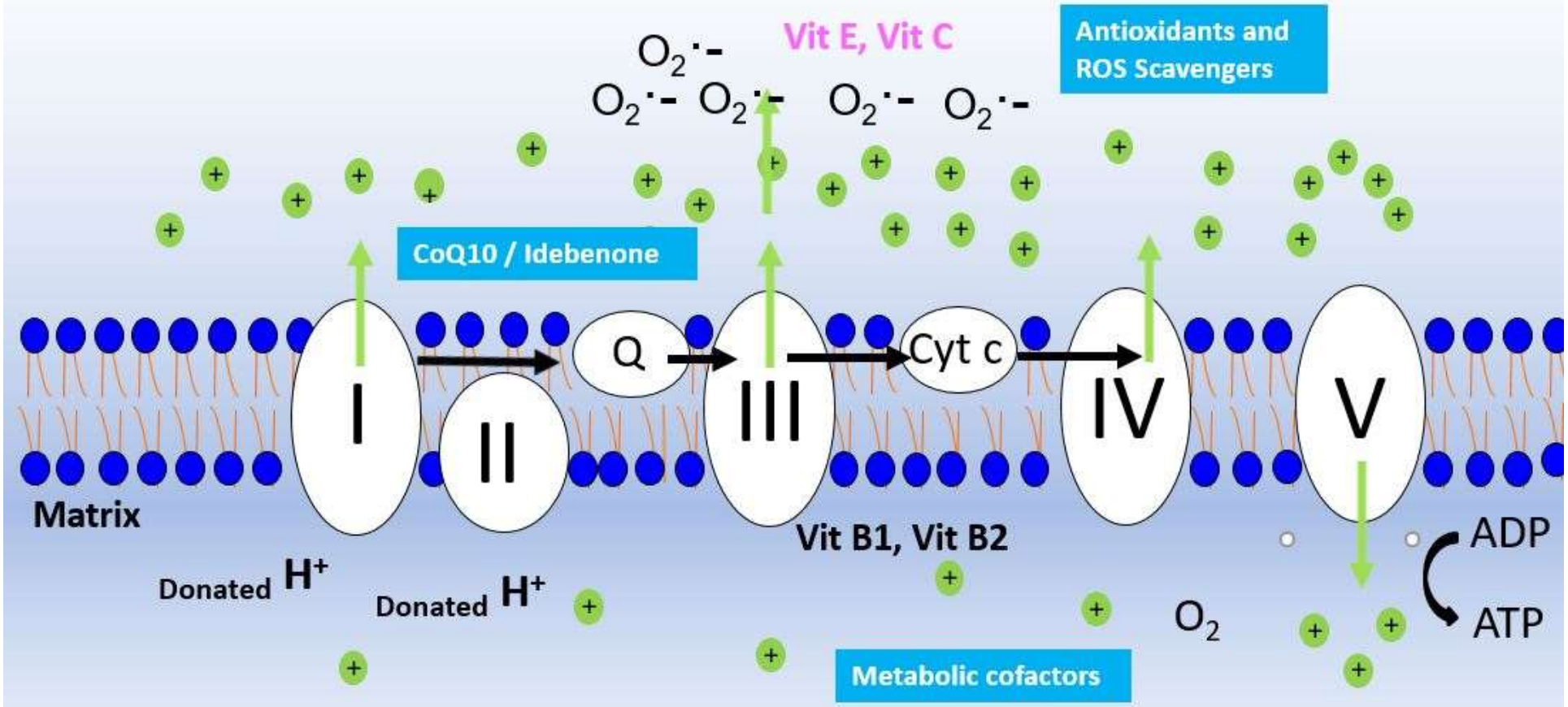
- Make ATP for cellular energy
  - Fats
  - Carbohydrates
  - Protein
- Participate in apoptosis
- Make free radicals
- ----



High mtDNA Mutation Rate

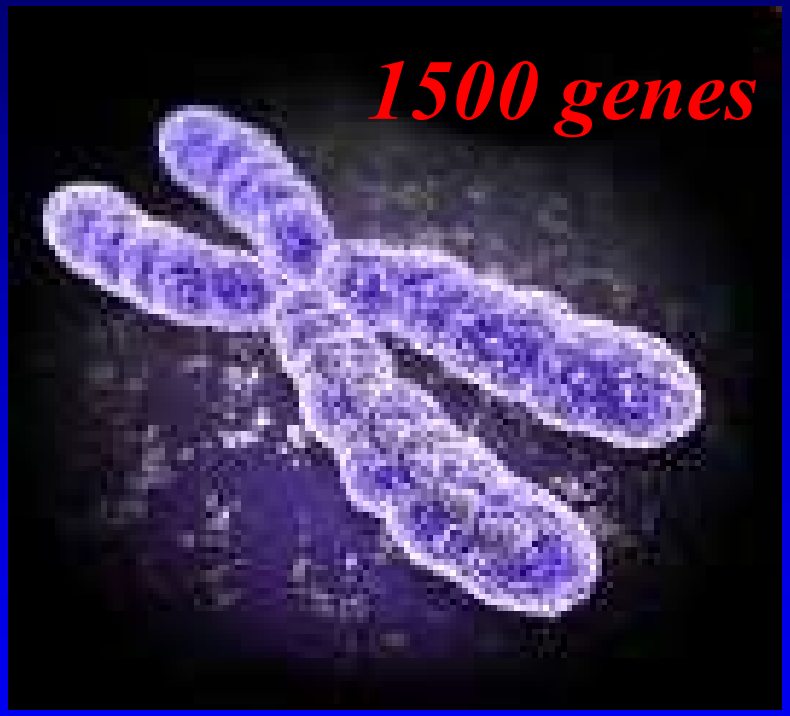
- High replicative index
- Limited efficiency of its repair mechanisms
- Oxidative microenvironment
- Lack of protective histones embracing this small DNA molecule

Electron Transport Chain

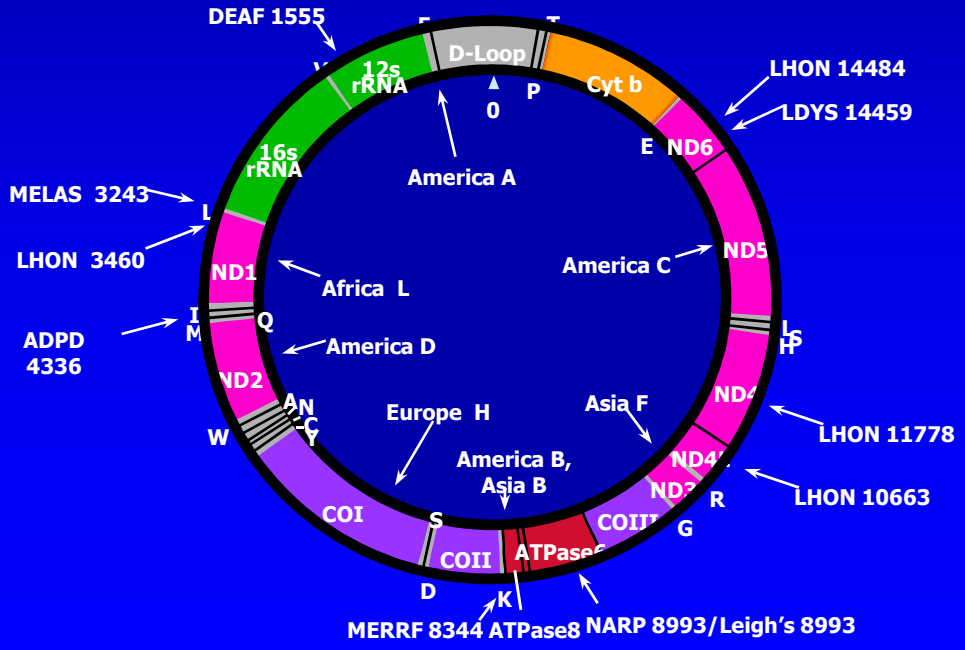


Two Genomes for One Organelle

MSOffice8



37 genes



Slide 9

MSOffice8 or "in one cell"
, 3/25/2013

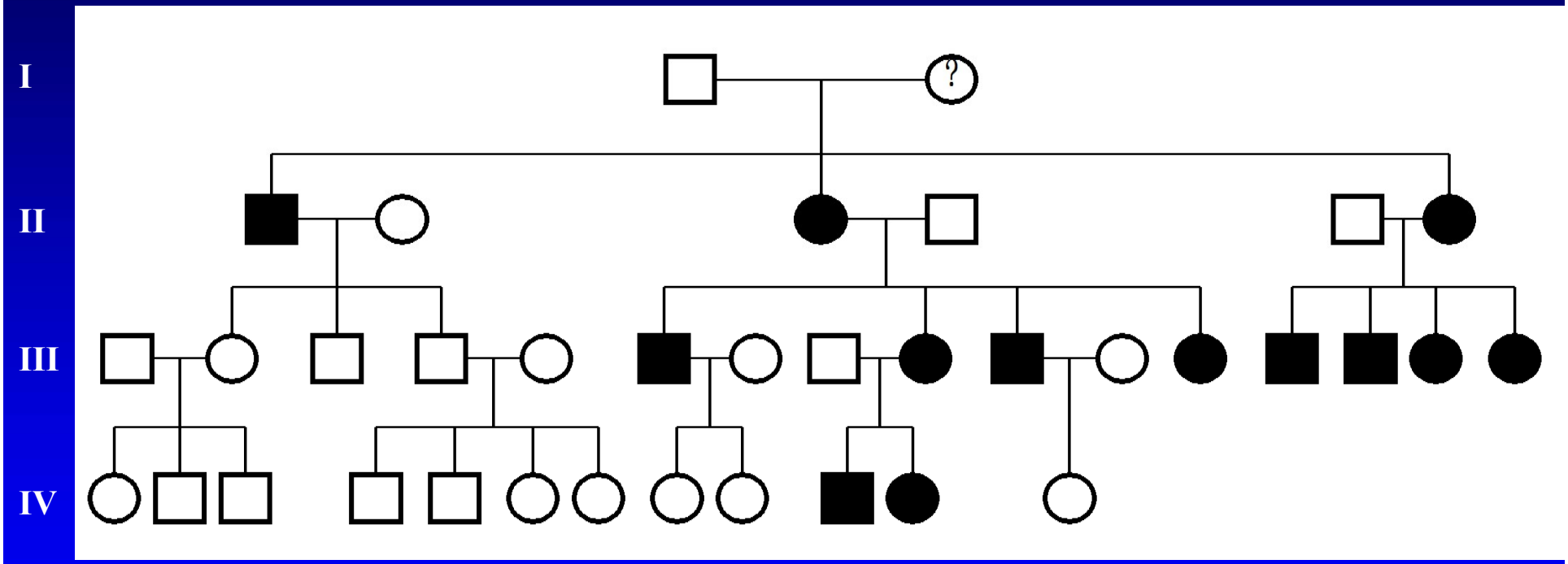
mtDNA

- Maternal Inheritance
- Heteroplasmy
- Replicative segregation
- High Mutation Rate

nDNA

- AD
- AR
- X-linked

Maternal Inheritance



Mitochondria & Aging

A Mathematical Model for the Diversity of Age-Related mtDNA Mutations

Huanzheng Li [1,2], Jesse Slone [3], Lin Fei [4,†] and Taosheng Huang [3,*,†]

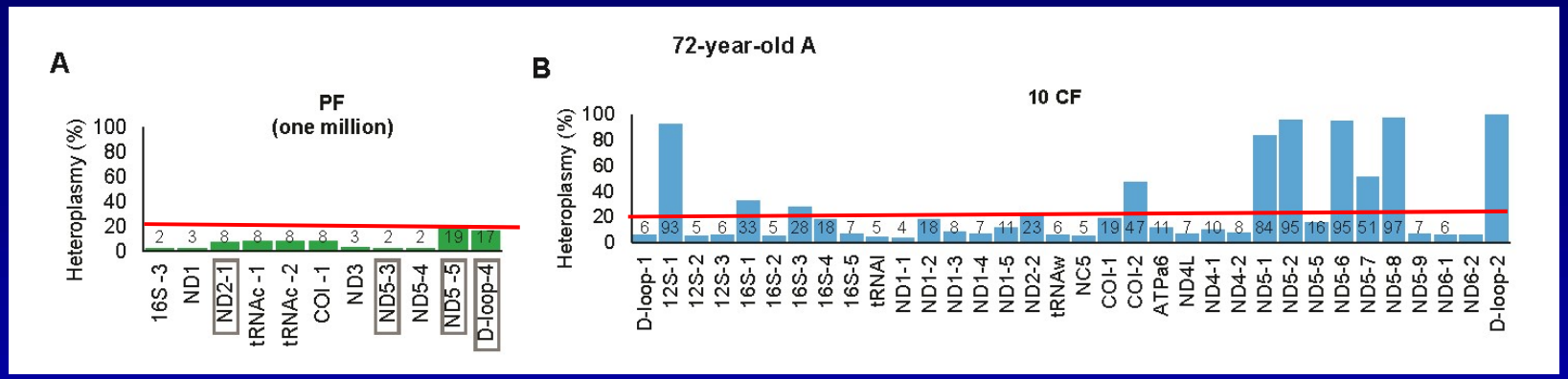
attention to the likely role that mtDNA mutation plays in aging and senescence. Finally, we will use this context to develop a mathematical formula for estimating for the accumulation of somatic mtDNA mutations with age. This resulting model shows that almost 90% of non-proliferating cells would be expected to have at least 100 mutations per cell by the age of 70, and almost no cells would have fewer than 10 mutations, suggesting that mtDNA mutations may contribute significantly to many adult onset diseases.

$$B = 16{,}569Z\,(X_1 + X_2 + X_3)\,\mu/2$$

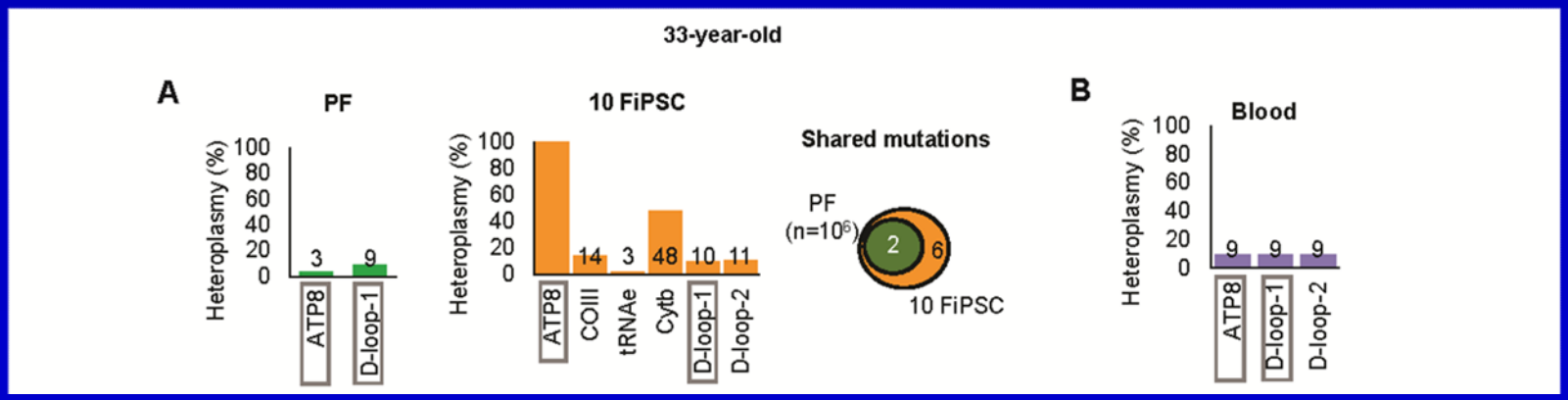
Under this setting, assuming all variables are independent of each other, the expected mutation burden is,

$$\begin{aligned} E(B) &= 16{,}569 \cdot 10^{E(\log Z)}\, E(\mu/2)\,(E(X_1) + E(X_2) + E(X_3)) \\ &= 16{,}569 \times 1000 \times 1.47 \times 10^{-7} \times (45 + 280 + 91) = 1013 \end{aligned}$$

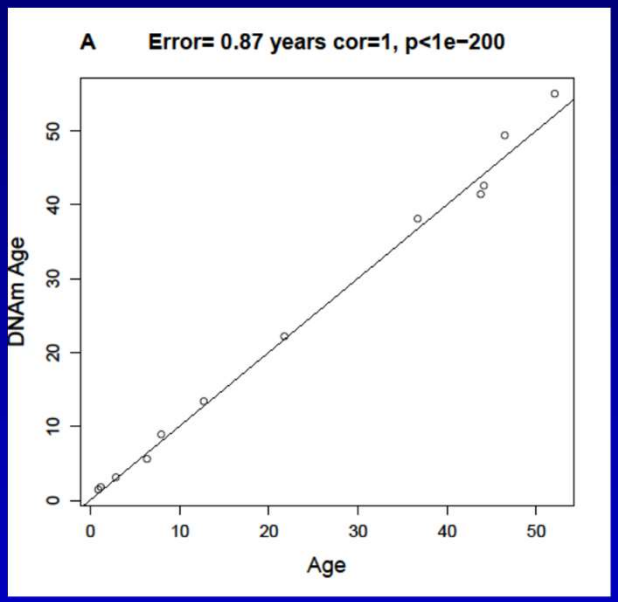
mtDNA Mutations in Skin Fibroblasts & iPSC Lines of a 72-year-old

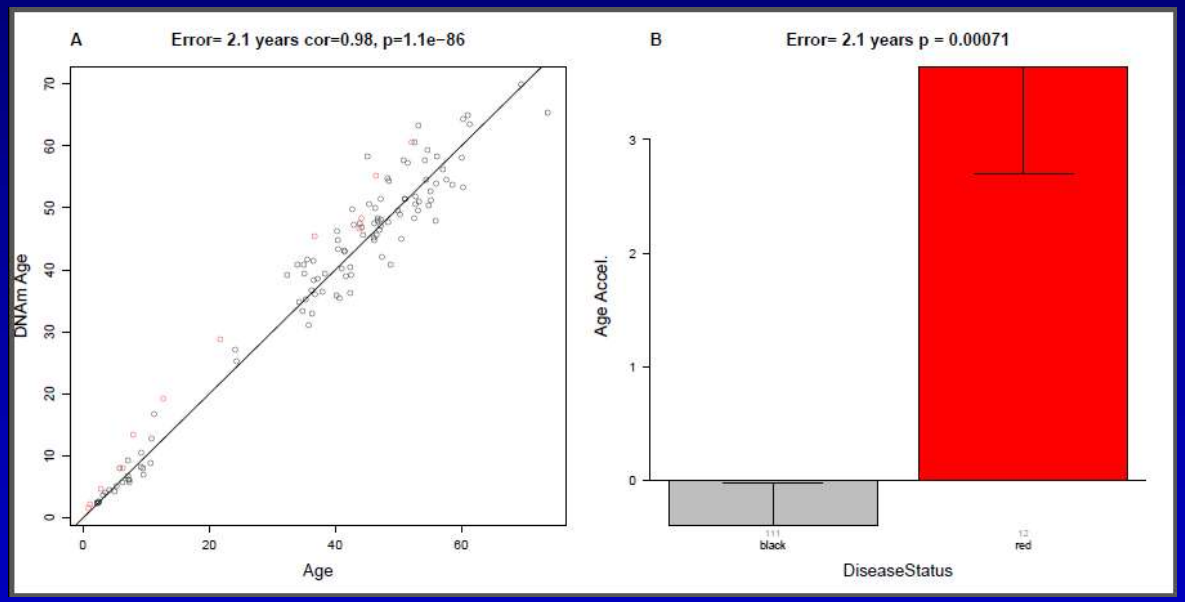


mtDNA Mutations in Young Subjects (Cell Stem Cell, 2016)

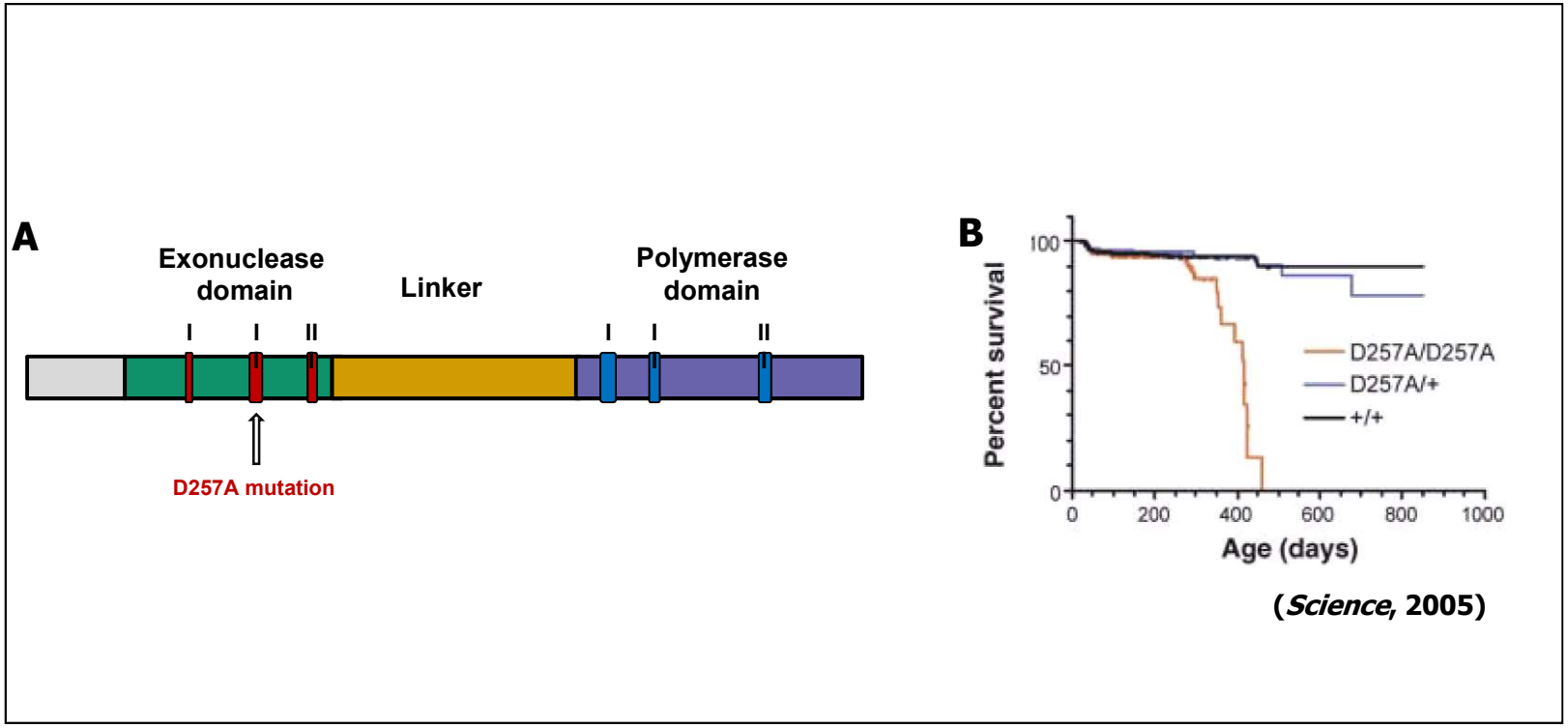


DNA Age (Horvath Clock) & mtDNA Mutation





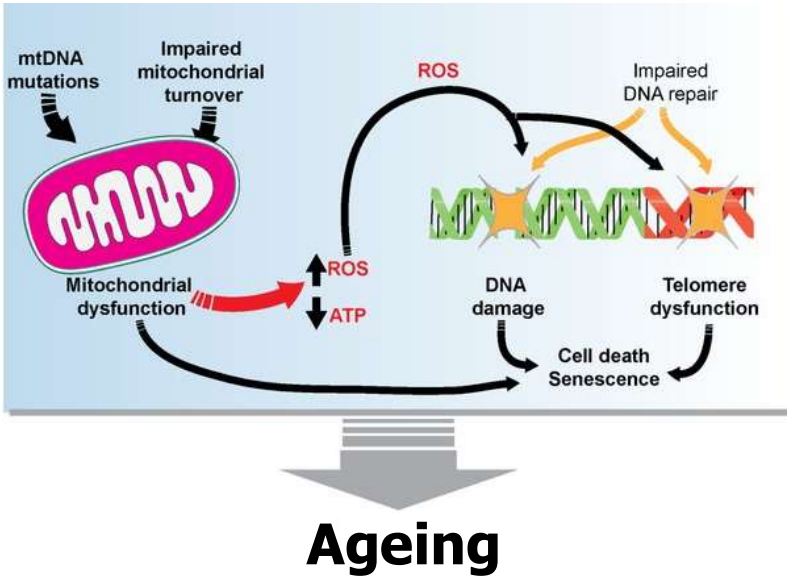
POLG and *Polg*$^{D257A/D257A}$ (*Polg*$^{mut/mut}$) Mutation



POLG (DNA polymerase subunit gamma) is the only known enzyme involved in mtDNA replication and repair.

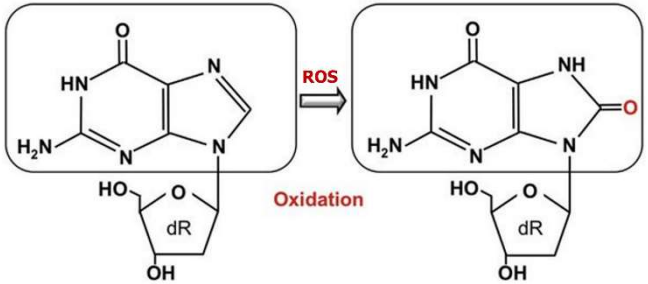
Mitochondrial Regulation of Aging

A

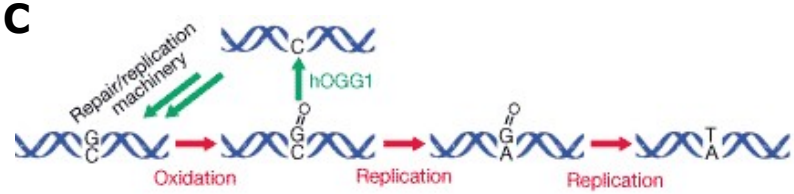


(*Circulation Research*, 2013)

B

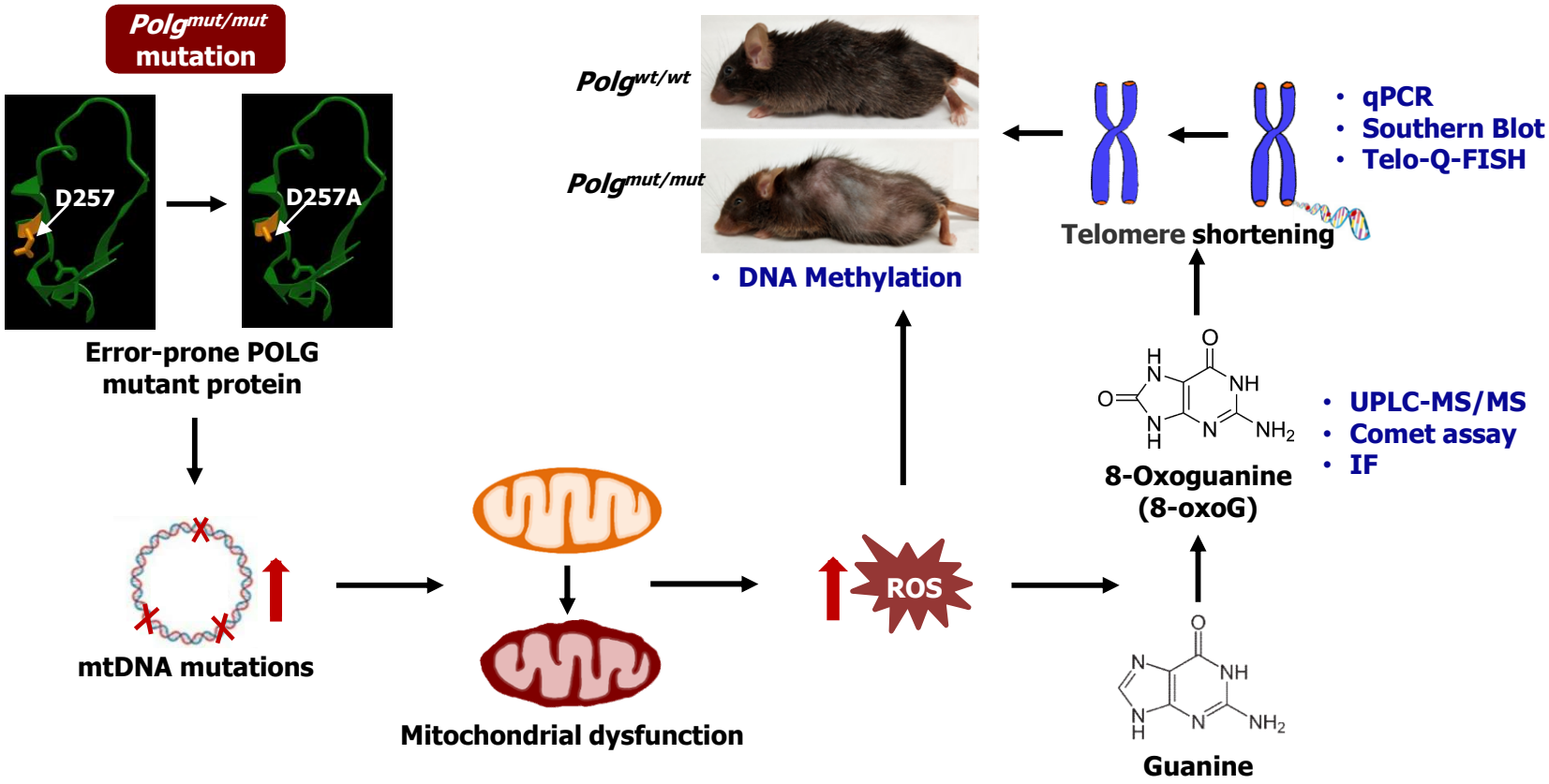


C



(*Nature*, 2000)

Hypothesis: *Polg*$^{mut/mut}$ Accelerates Aging by Elevated ROS



RESEARCH

RESEARCH ARTICLE SUMMARY

EVOLUTIONARY BIOLOGY

DNA methylation networks underlying mammalian traits

Amin Haghani *et al.*

A. Haghani et al., Science 381, eabq5693 (2023). DOI: 10.1126/science.abq5693

Article

Organ aging signatures in the plasma proteome track health and disease

https://doi.org/10.1038/s41586-023-06802-1

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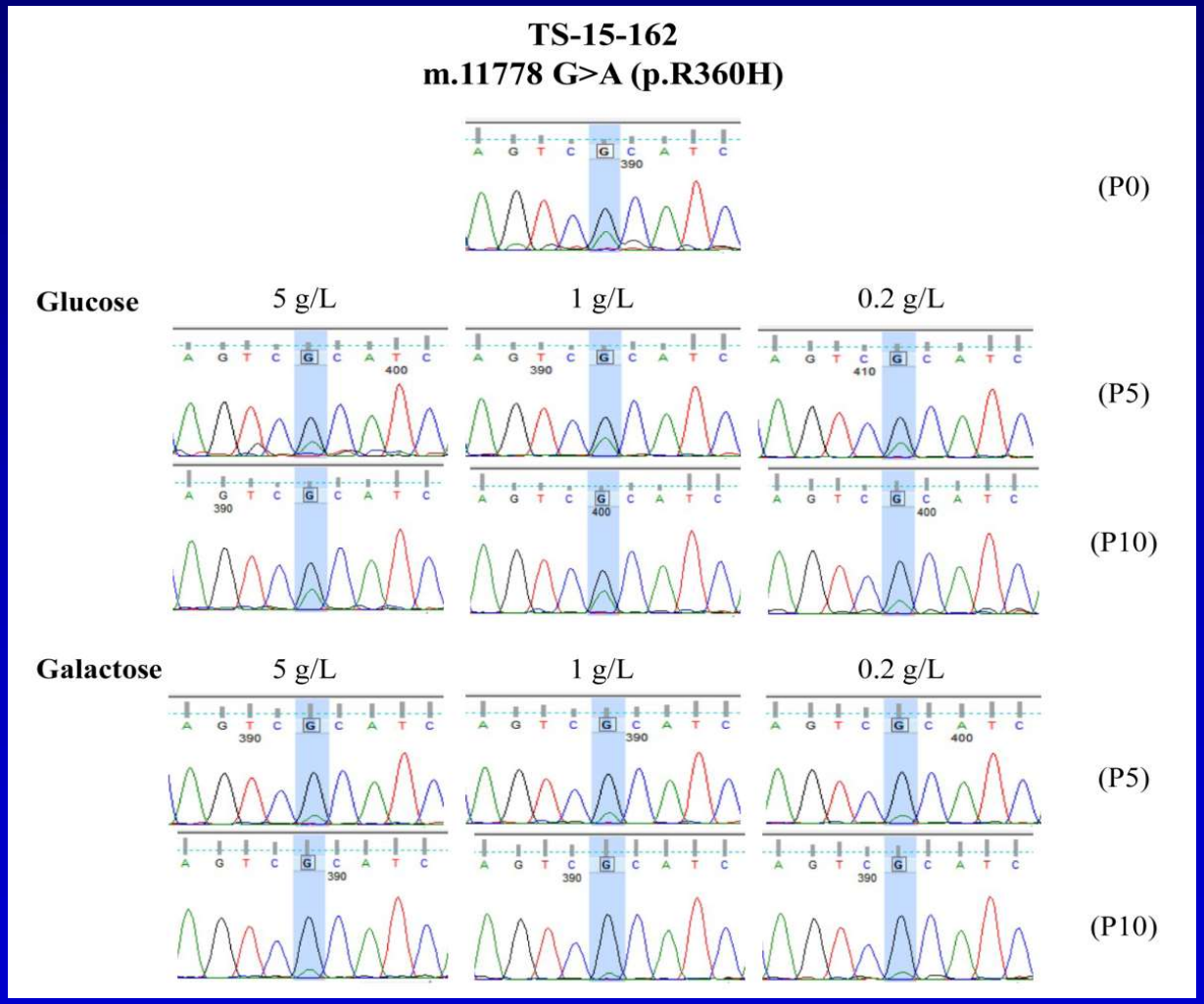
Open access

Check for updates

Hamilton Se-Hwee Oh[1,2,3,22], Jarod Rutledge[2,3,4,22], Daniel Nachun[5], Róbert Pálovics[2,3,6], Olamide Abiose[3,6], Patricia Moran-Losada[2,3,6], Divya Channappa[2,3,6], Deniz Yagmur Urey[2,7], Kate Kim[2,3,6], Yun Ju Sung[8,9], Lihua Wang[8,9], Jigyasha Timsina[8,9], Dan Western[8,9,10], Menghan Liu[8,9], Pat Kohlfeld[8,9], John Budde[8,9], Edward N. Wilson[3,6], Yann Guen[6,11], Taylor M. Maurer[5], Michael Haney[2,3,6], Andrew C. Yang[12,13,14], Zihuai He[6], Michael D. Greicius[6], Katrin I. Andreasson[3,6,15], Sanish Sathyan[16], Erica F. Weiss[17], Sofiya Milman[16], Nir Barzilai[16], Carlos Cruchaga[8,9], Anthony D. Wagner[3,18], Elizabeth Mormino[6], Benoit Lehallier[6], Victor W. Henderson[3,6,19], Frank M. Longo[3,6], Stephen B. Montgomery[5,20,21] & Tony Wyss-Coray[2,3,6] ✉

Animal studies show aging varies between individuals as well as between organs within an individual[1–4], but whether this is true in humans and its effect on age-related diseases is unknown. We utilized levels of human blood plasma proteins originating from specific organs to measure organ-specific aging differences in living individuals. Using machine learning models, we analysed aging in 11 major organs and estimated organ age reproducibly in five independent cohorts encompassing 5,676 adults across

Nutrition on Heteroplasmy Shift



Current Huang Laboratory Projects

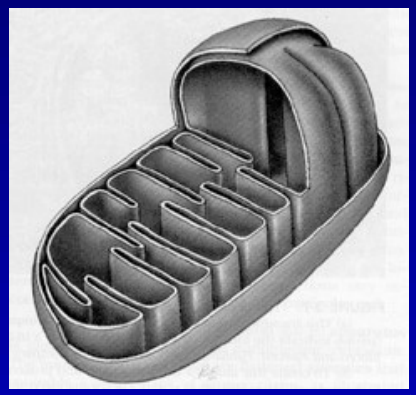
Paternal Inheritance

Luo et al *PNAS*, 2018

mtDNA

Ma et al Nature , 2015
Kang et al, Nature , 2016
Zhang et al, Rep BioMed 2017

Kang et al Cell Stem Cell, 2016



Optic Atrophy *OPA1*

- Human Mutation
- Drosophila Model
- Mouse Model
- IPS cells and ES cells

(Stem Cell, 2013, Stem Cell Translation Medicine, 2015)

Lenz Syndrome
New Syndrome
NAA10 (JMG, 2014)

Molecular Diagnostic Laboratory

Optic nerve atrophy & axonal peripheral neuropathy
SLC25A46
Abrahams et al *Nat Genet, 2015*
Li et al, HMG, 2017
Li et al 2020

ACACB
ATP5G3

Leigh syndrome & Hearing loss
NARS2
Simons et al, Plos Genet, 2015

DHTKD1 & *OGDHL*
Sherrill et al *JCI Insight 2018*

FDXR
Peng et al, HMG, 2017,
Slone et 2018, 2020; Li et al 2020

Thanks

Questions ?