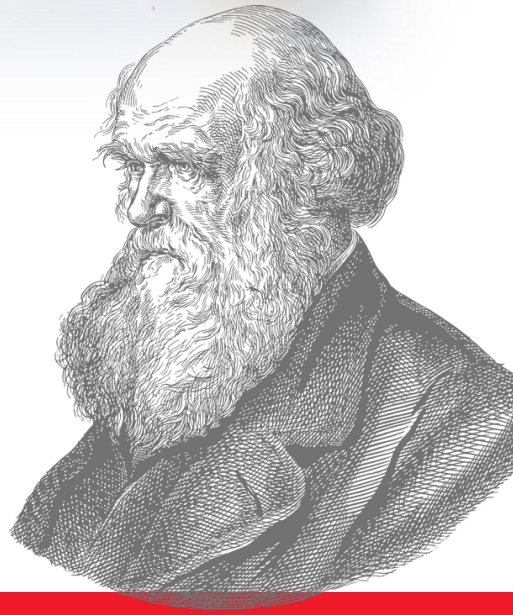
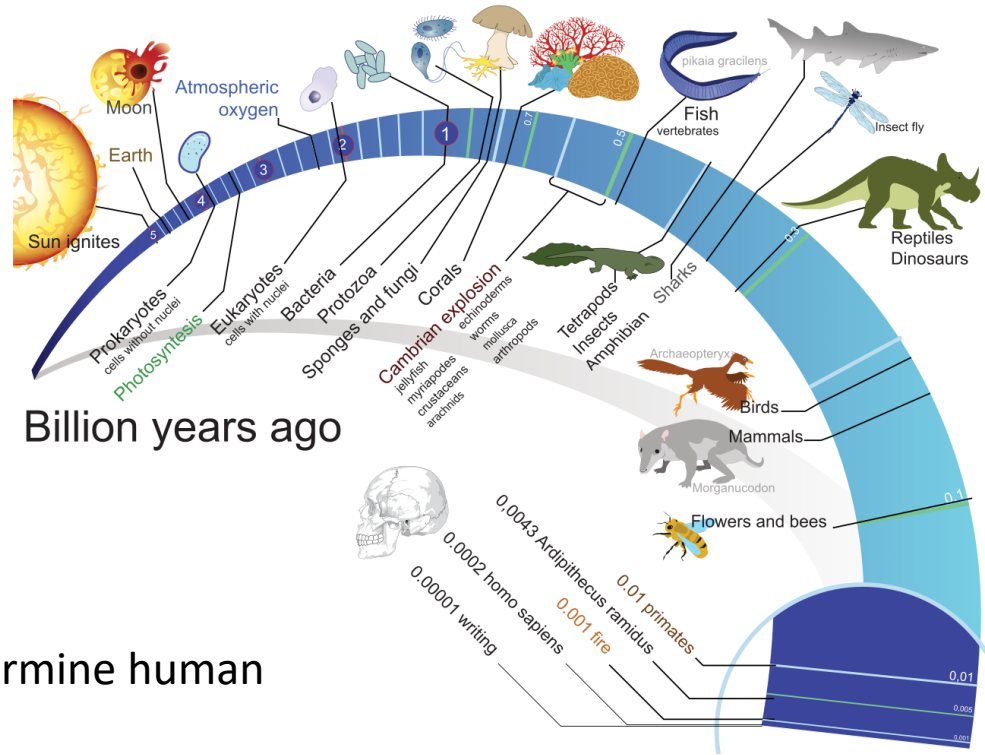
MUNI
MED

Evolutionary medicine



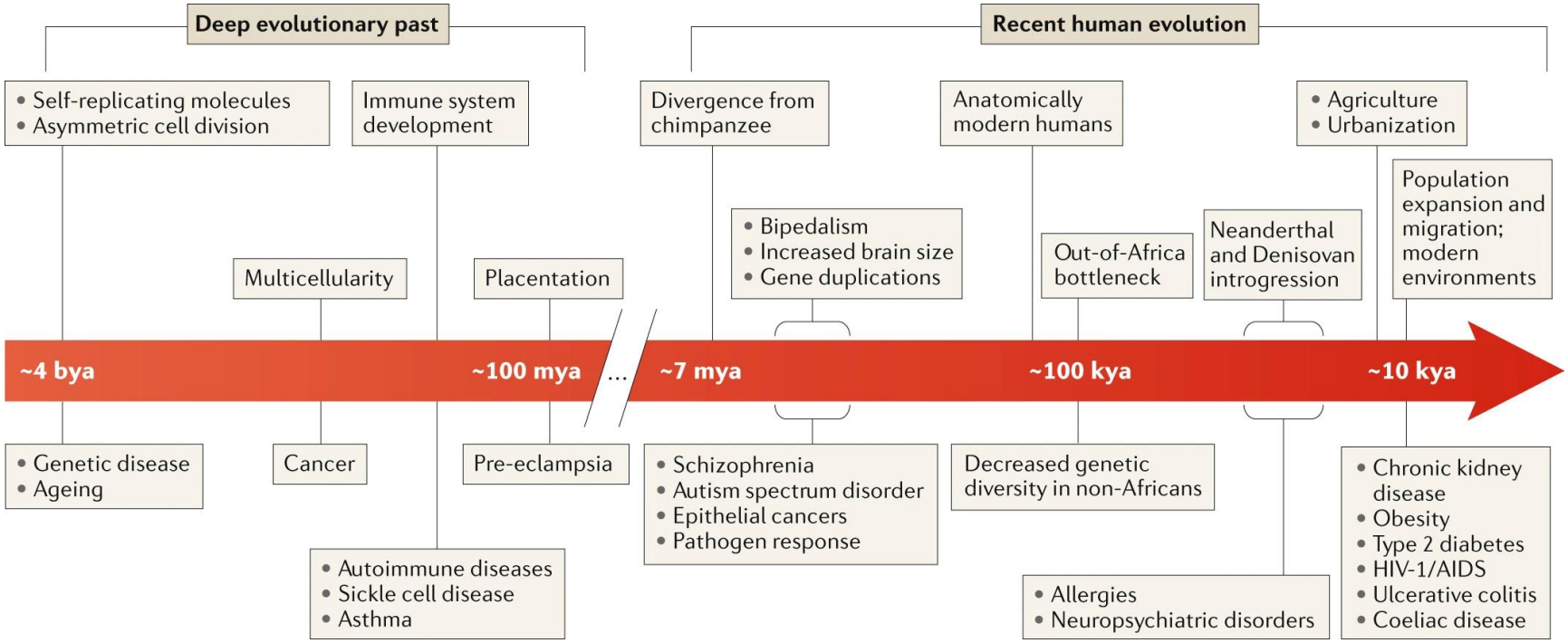
Petr Müller

Evolutionary medicine is the study of how evolutionary processes have produced human traits/disease and how evolutionary principles can be applied in medicine.



- Timeline of evolutionary events that determine human diseases
- Evolution and non-genetic adaptation to enviromental changes - lifestyle changes and the effect of cultural evolution
- Evolutionary pressure and adaptation in other animal species
- Evolutionary trade-offs and and civilization diseases

A timeline of evolutionary events →



A timeline patterns of human disease risk →

Evolutionary medicine and genetic diseases

How evolutionary medicine explains complex genetic diseases

1. **natural selection does not result in perfect bodies but operates on relative reproductive fitness**

2. **mismatch between our biological legacy and our modern environments**

3. **trade-offs, the idea that there are combinations of traits that cannot be simultaneously optimized by natural selection**

4. **evolutionary conflicts. Traits expressed by complex metazoans are a balanced compromise between different genetic elements and bodily systems**


NATURE REVIEWS | GENETICS VOLUME 22 | MAY 2021 | 269

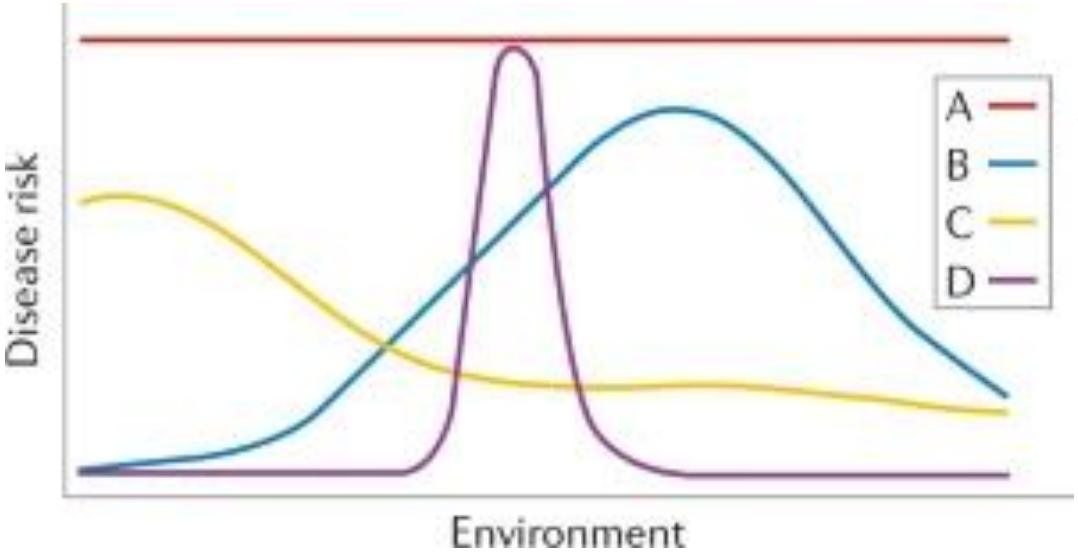
The influence of evolutionary history on human health and disease

Mary Lauren Benton[1,2], Abin Abraham[3,4], Abigail L. LaBella[5], Patrick Abbot[5], Antonis Rokas[1,3,5] and John A. Capra[1,5,6]✉

The evolutionary necessity of disease / the impact of environment

Reaction norms

Representations of how the expressed phenotype for a genotype varies in response to a range of environments.

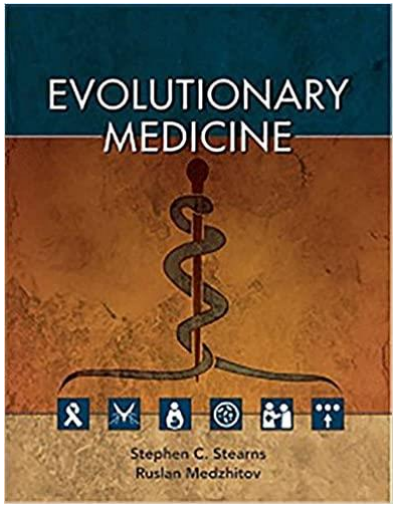


genotypes lead to disease in all environments

Most diseases fall between these extremes (lines B and C)

specific pairing of environment and genotype

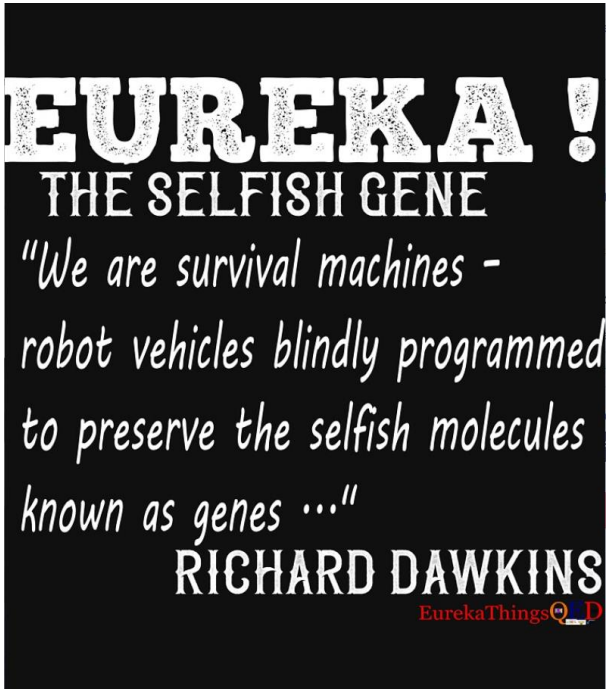
Viewing disease through the lens of evolution provides a flexible and powerful framework for defining and classifying disease.



Gene-centered view of evolution

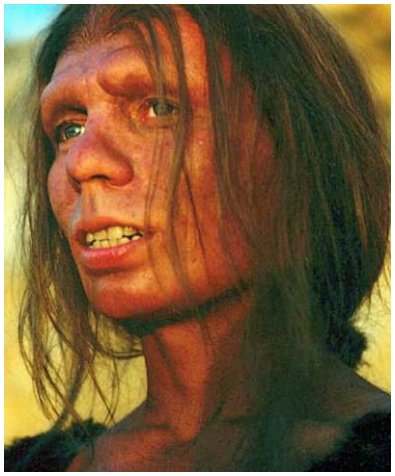
natural selection does not result in perfect bodies but operates on relative reproductive fitness

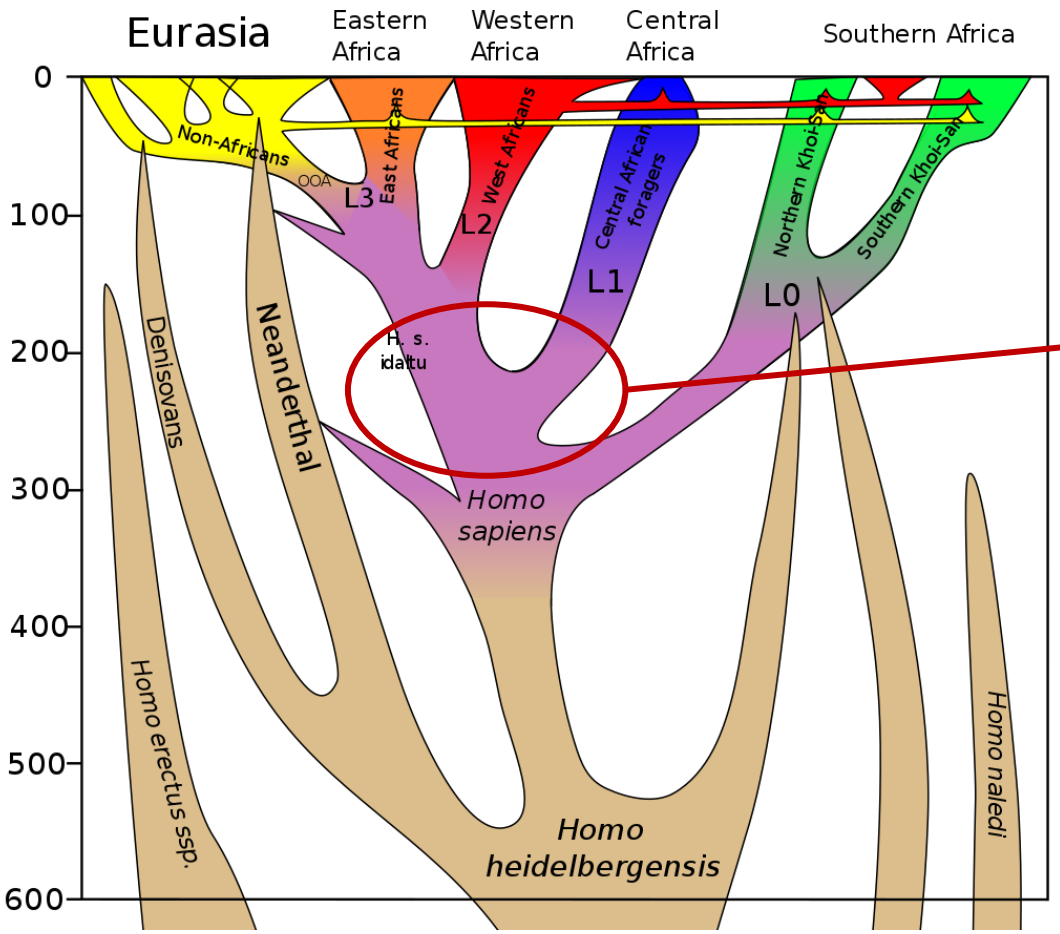
"Selfish gene theory"



- Altruism, cooperation, suicide
- Transposons, genetic waste information
- Sexual selection vs. Natural selection

Interbreeding between archaic and modern humans





Higher genetic diversity cohabitation of non-relatives cooperation

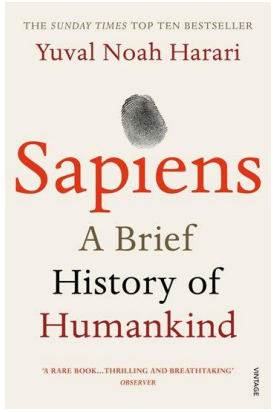
HLA-B*73 introgressed from Denisovans into modern humans in western Asia

Tibetan people EGLN1 and EPAS1 gene variant, associated with hemoglobin concentration

A model of the phylogeny of *H. sapiens* over the last 600,000 years (vertical axis).

Cultural evolution

is the idea that human cultural change—that is, changes in socially transmitted beliefs, knowledge, customs, skills, attitudes, languages, and so on—can be described as a Darwinian evolutionary process



Slaves to wheat: How a grain domesticated us

Unlike animals, the survival of humans is currently much less determined by their genetic information.

Much more important to human evolutionary fitness has become information obtained non-genetically

Neolithic revolution, cooperation and cultural evolution

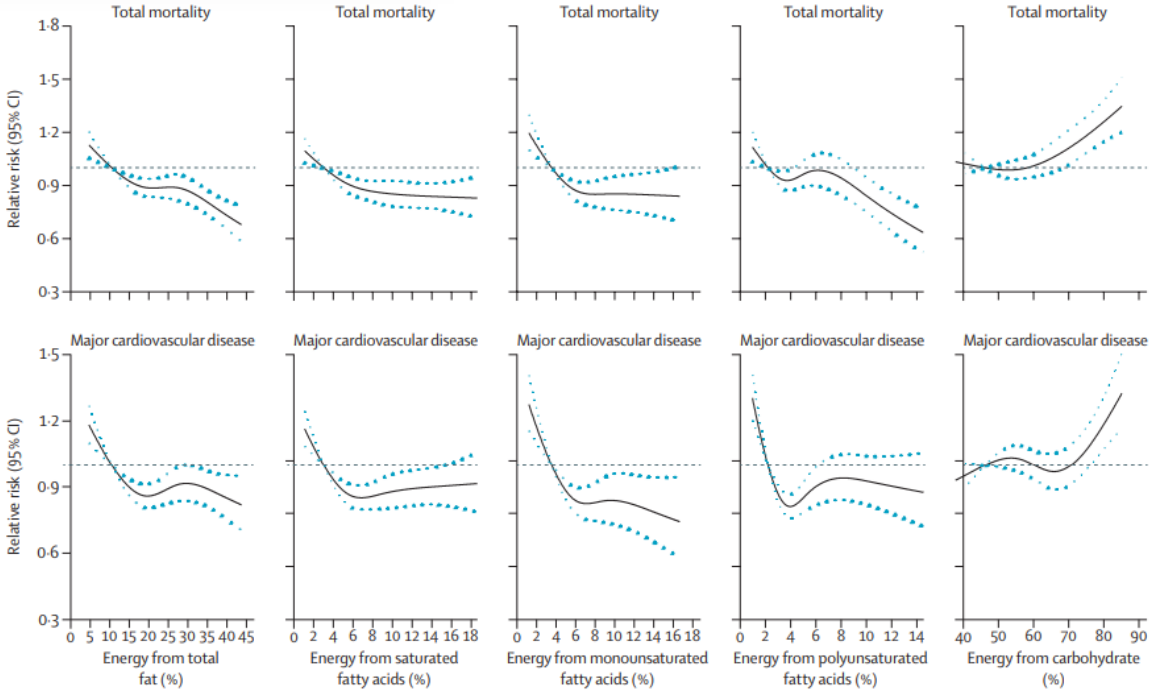
THE LANCET

Dietary carbohydrate intake and mortality: a prospective cohort study and meta-analysis

Sara B Seidelmann, Brian Claggett, Susan Cheng, Mir Henglin, Amil Shah, Lyn M Steffen, Aaron R Folsom, Eric B Rimm, Walter C Willett, Scott D Solomon

Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study

Mahshid Dehghan, Andrew Mente, Xiaohe Zhang, Sumathi Swaminathan, Wei Li, Viswanathan Mohan, Romaina Iqbal, Rajesh Kumar,

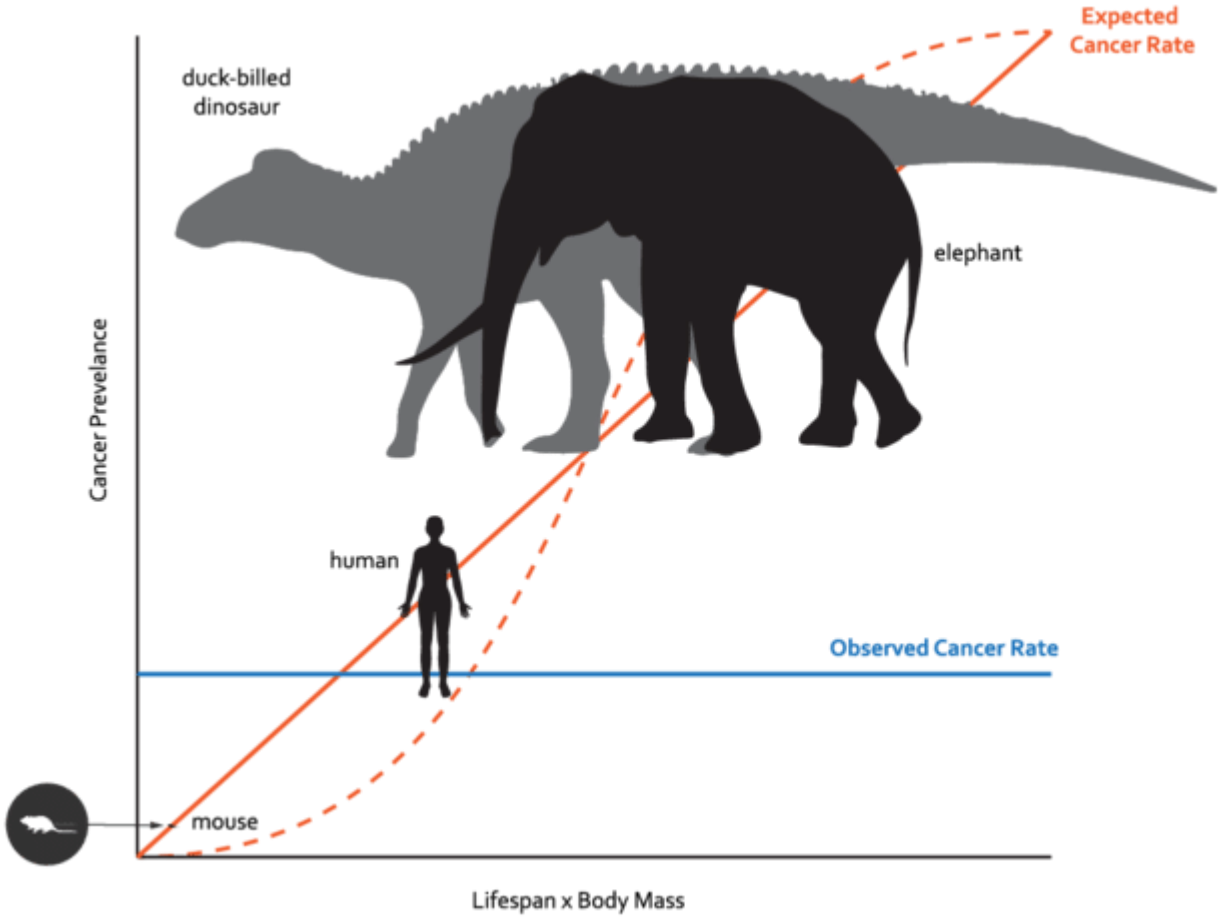


Mechanisms of evolutionary adaptations in different animal species
The traits related to common human diseases

- Cancer
- Ageing
- Pathogen/infection resistance

Cancer and Peto's paradox

- the incidence of cancer does not appear to correlate with the number of cells in an organism
- In order to build larger and longer-lived bodies, organisms required greater cancer suppression.



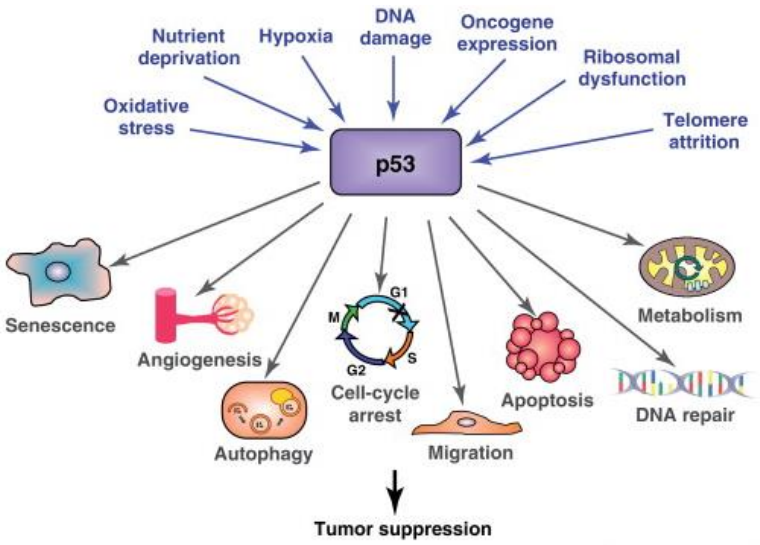
Evolutionary „trade off“:

Body size vs. risk of cancer

Gene Quantity in Cancer

HUMANS vs. ELEPHANTS

71 years	*average lifespan*	65 years
62 kg	*weight*	4800 kg
37.2 trillion	*number of cells*	3.72 quadrillion
11–25%	*cancer mortality*	4.81%
2	*copies of p53*	40



Mice altered to express "always-on" active TP53 exhibited increased tumor suppression ability, but also showed signs of premature aging. (TP53 cannot be the only explanation)

Balance of protein production and its regulation

Injury

Infection

Interspecies and intraspecies competition

Lack of food

Growth factor

mTOR signalling

AMPK activation

Glucocorticoid signalling

Starvation Autophagy

Make more protein

Protein synthesis inhibition

Protein aggregation

Fitness

Adaptive immunity

Cancer

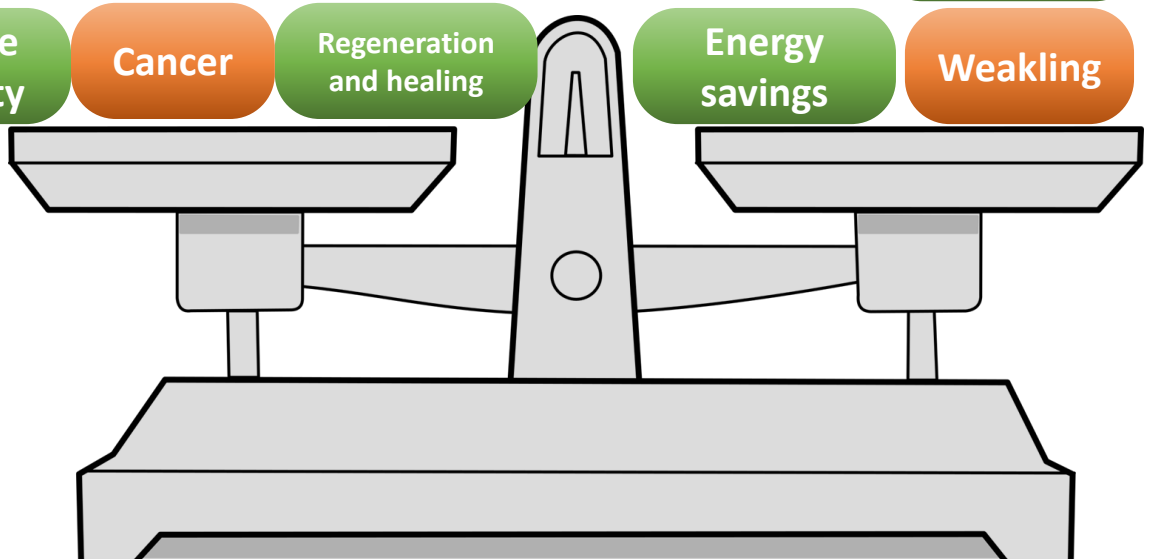
Regeneration and healing

Immunocompromised

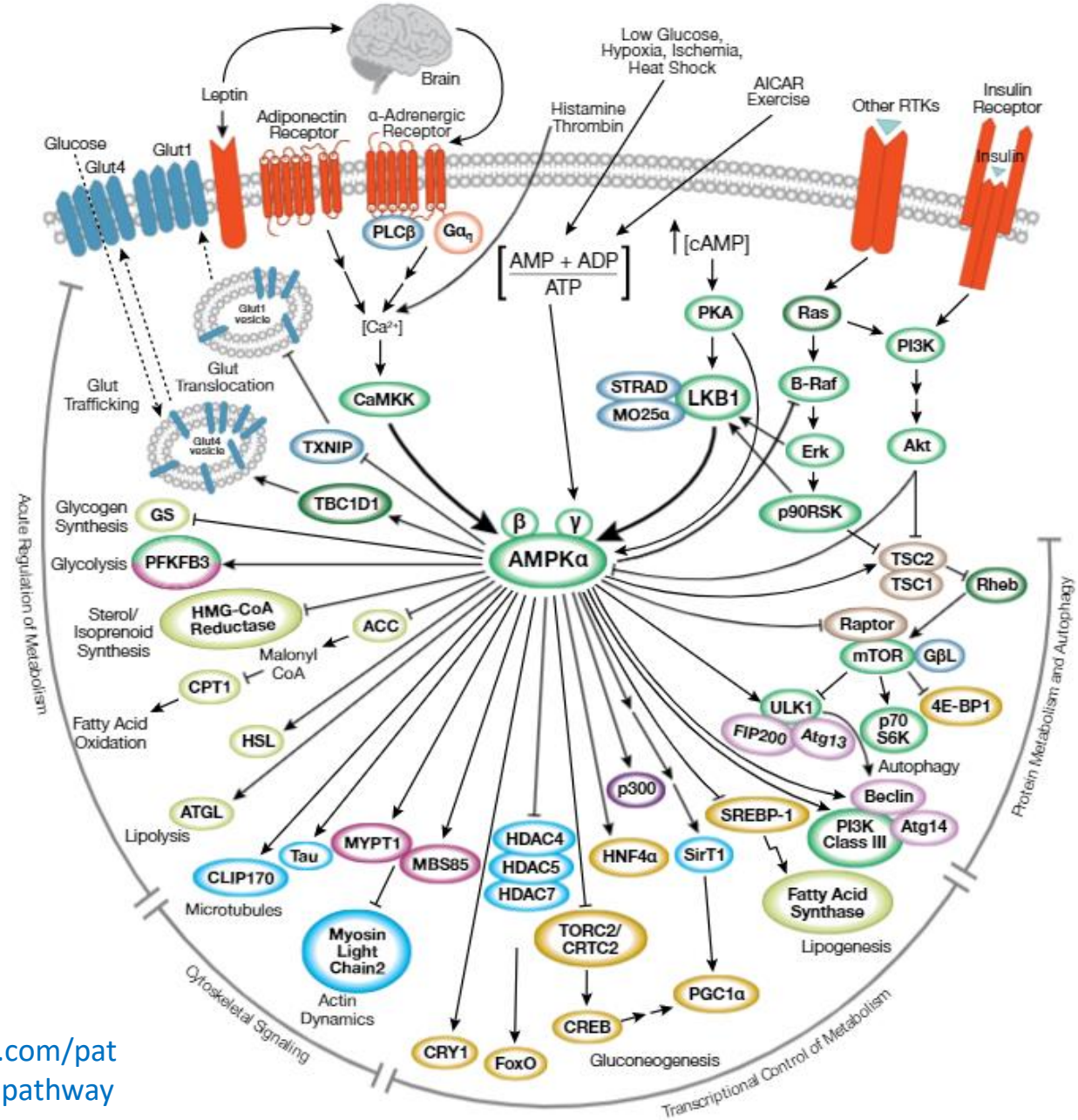
Longevity

Energy savings

Weakling



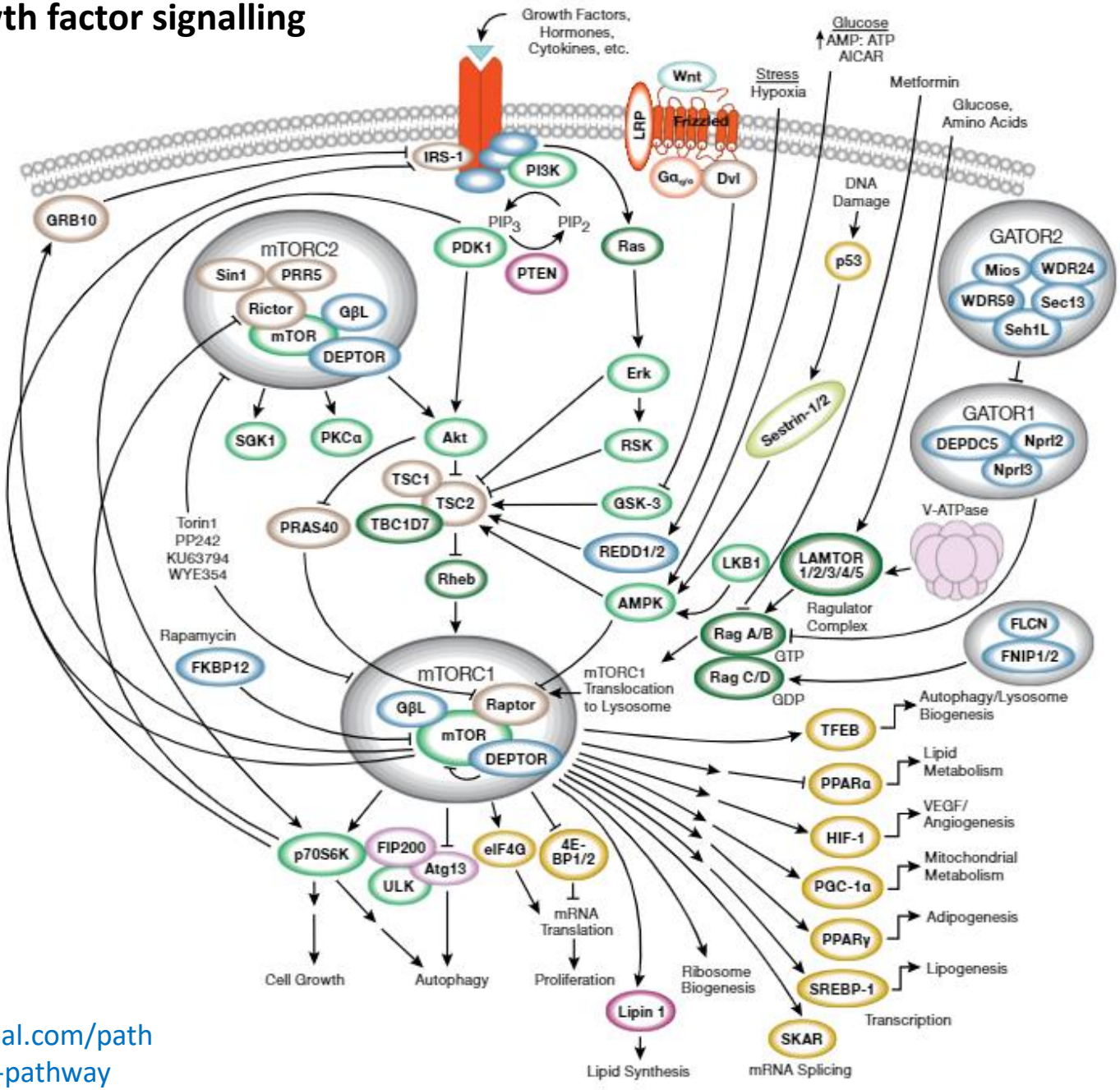
AMPK signalling



Autophagy

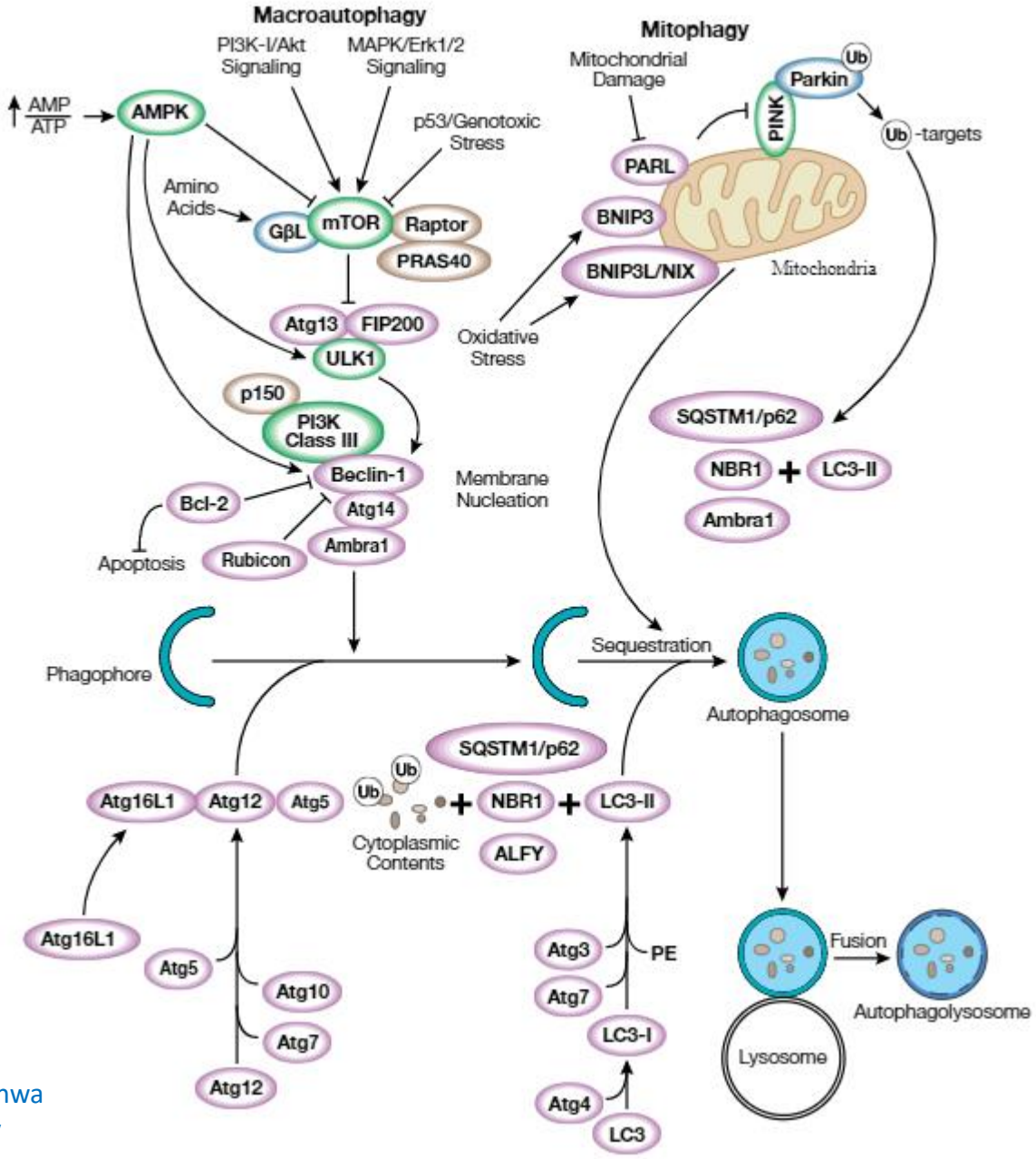
https://www.cellsignal.com/pathways/ampk-signaling-pathway

mTOR and growth factor signalling



https://www.cellsignal.com/pathways/mtor-signaling-pathway

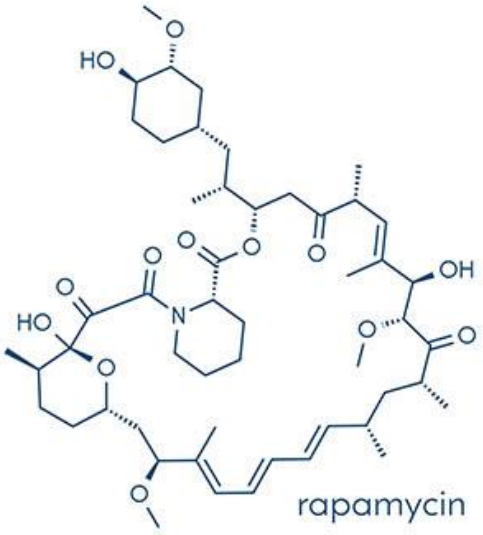
Autophagy

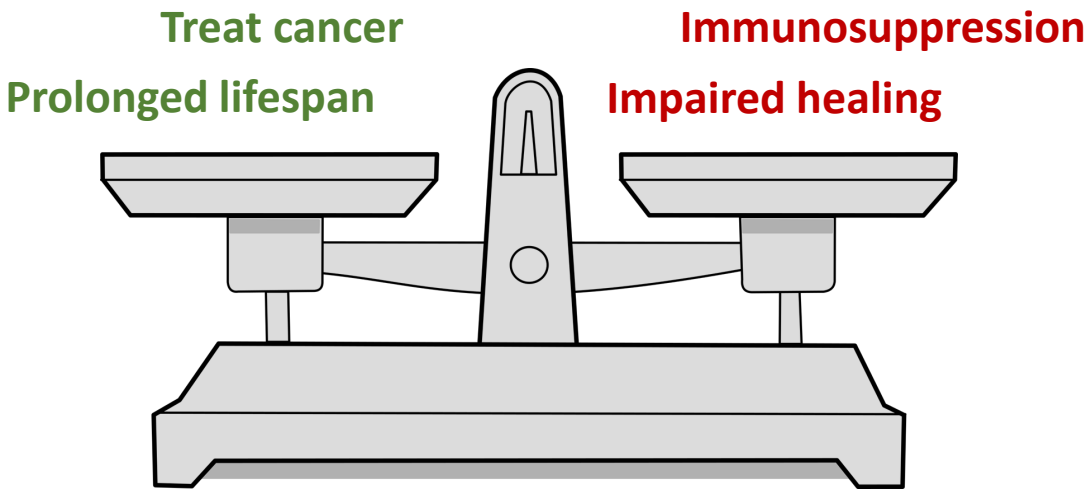


https://www.cellsignal.com/pathways/autophagy-signaling-pathway

How can we affect protein homeostasis ?

- Georges Nógrády was trying to understand why the inhabitants of Easter Island, despite walking around barefoot
- The Ayerst Pharmaceuticals team was able to identify a new antifungal compound in the soil samples that was produced by the bacterium Streptomyces hygroscopicus
- **Identification of the mTOR Signaling Network**
- Rapamycin's eventual development into a clinical compound (Rapamune), used to prevent organ transplant rejection and treatment for some cancers

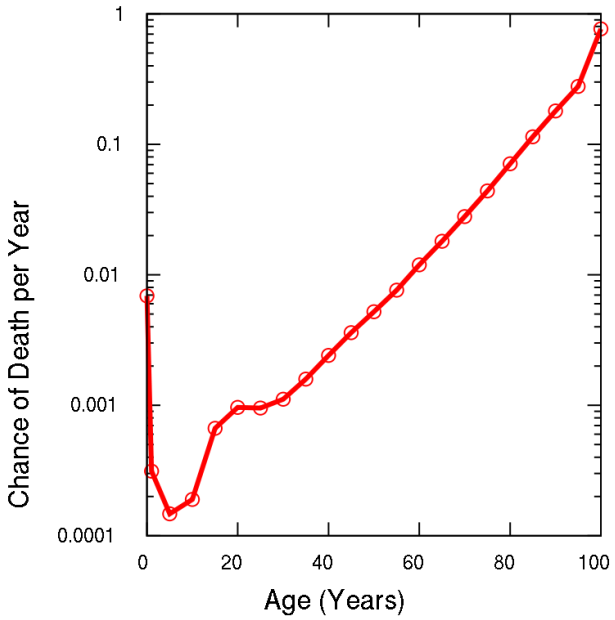


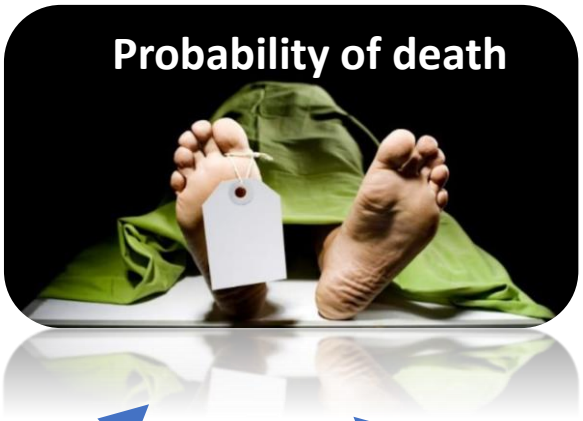


https://www.bio-rad-antibodies.com/blog/history-of-rapamycin.html

Gompertz–Makeham law of mortality

Estimated probability of a person dying at each age, for the U.S. in 2003. Mortality rates increase exponentially with age after age 30.





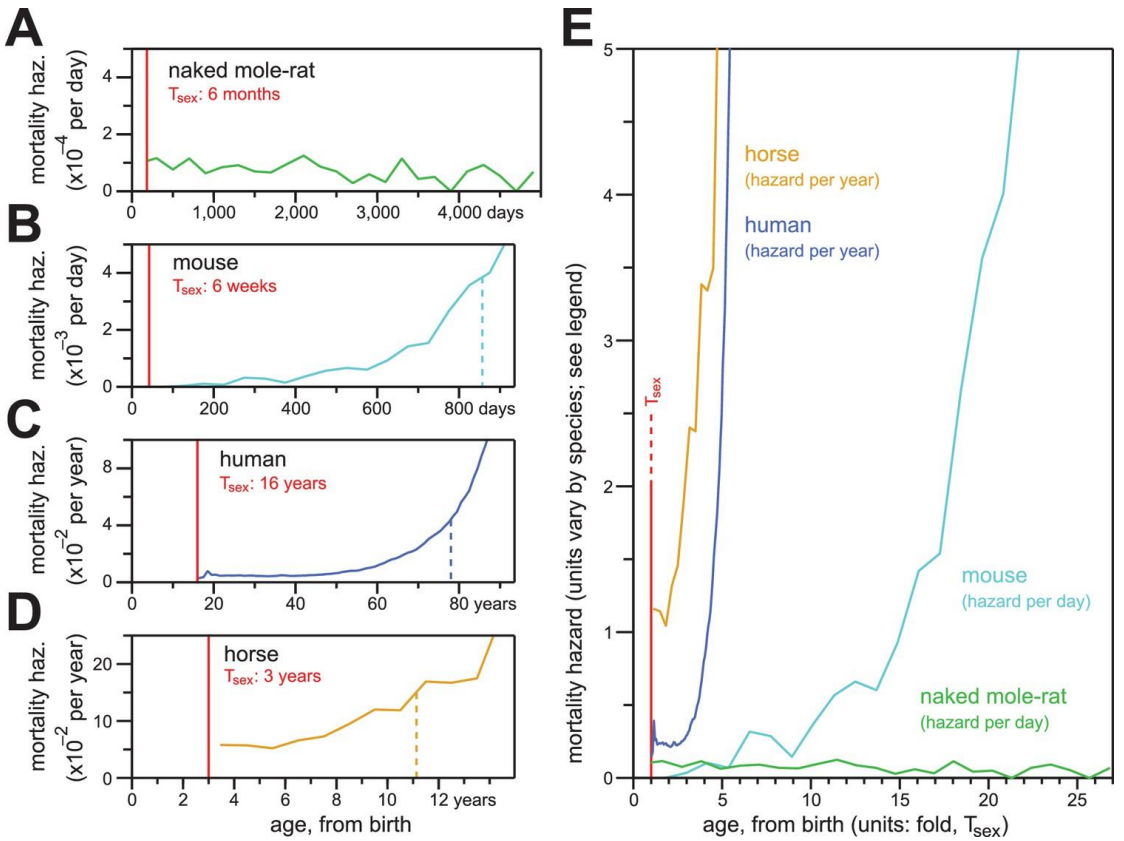
age-independent component

The Gompertz–Makeham law states that the human death rate is the sum of an **age-dependent component** (the Gompertz function, named after Benjamin Gompertz), which increases exponentially with age and an **age-independent component** (the Makeham term, named after William Makeham).

Naked mole rats defy the biological law of aging (Heterocephalus glaber)

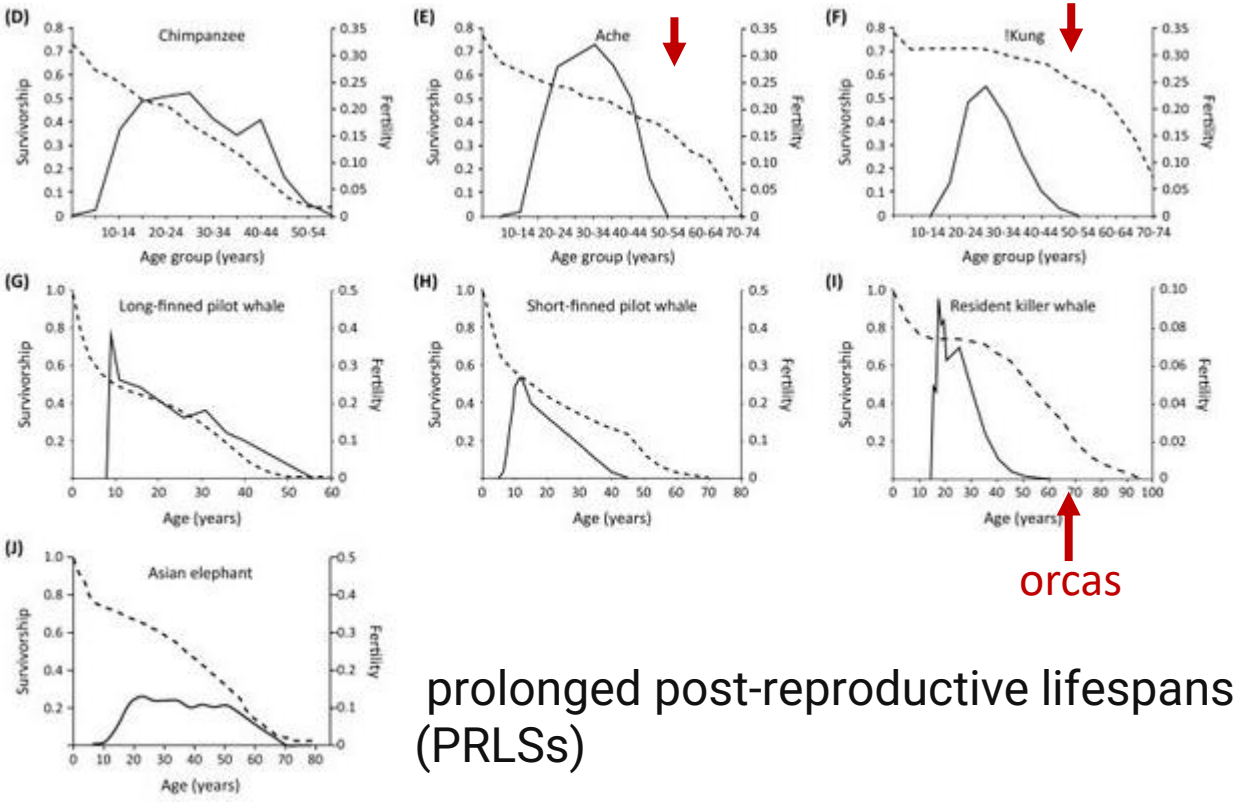
- rarely get cancer
- resistant to some types of pain
- survive up to 18 minutes without oxygen.

In contrast to the mortality hazards of other mammals, which increased with chronological age, the mortality hazard of naked mole-rats remained constant.



The evolution of prolonged life after reproduction

primitive indigenous people



orcas

prolonged post-reproductive lifespans (PRLSs)

Mechanisms of innate immunity

(fast but non-specific response)

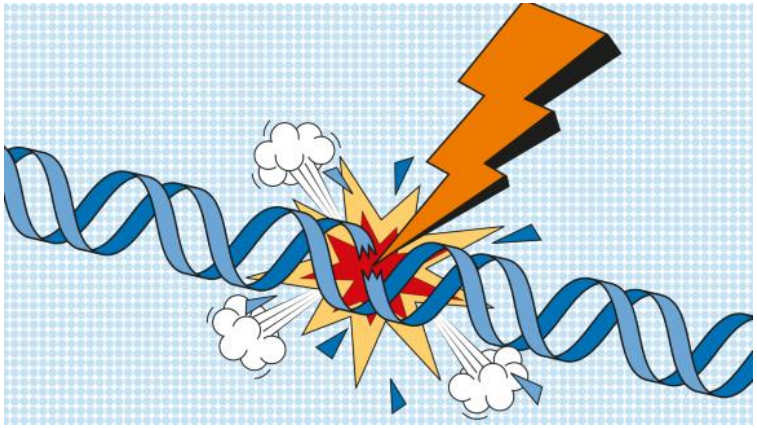
Detection of pathogenic microorganisms

- Membrane receptors
- Intracellular receptors of foreign nucleic acids
- Cytokine signalling

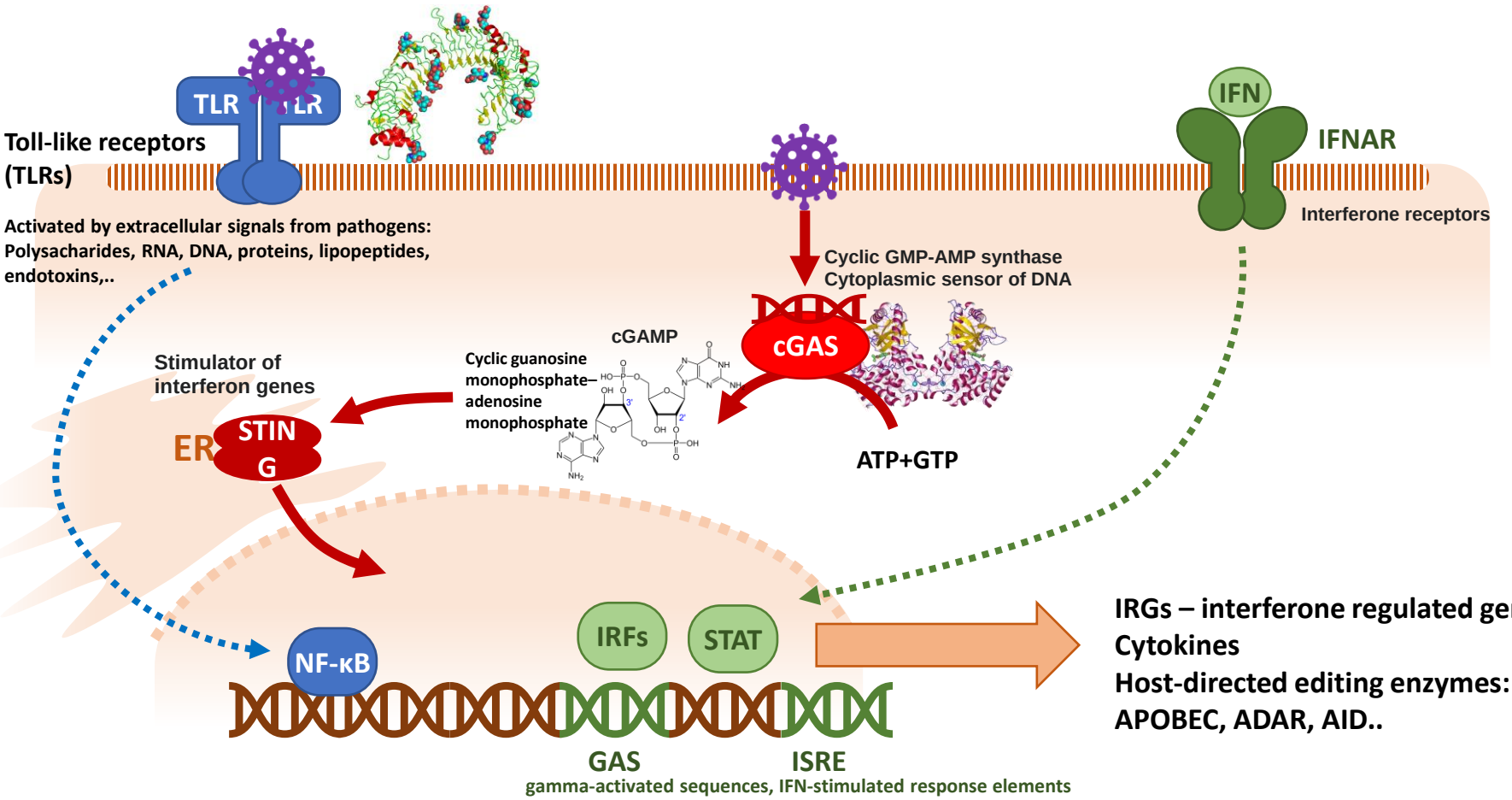
Intracellular signalling pathways

Activation of transcription / gene expression

- Expression of cytokines
- Activation of specific immune response
- Elimination of microorganisms
- Use of gene



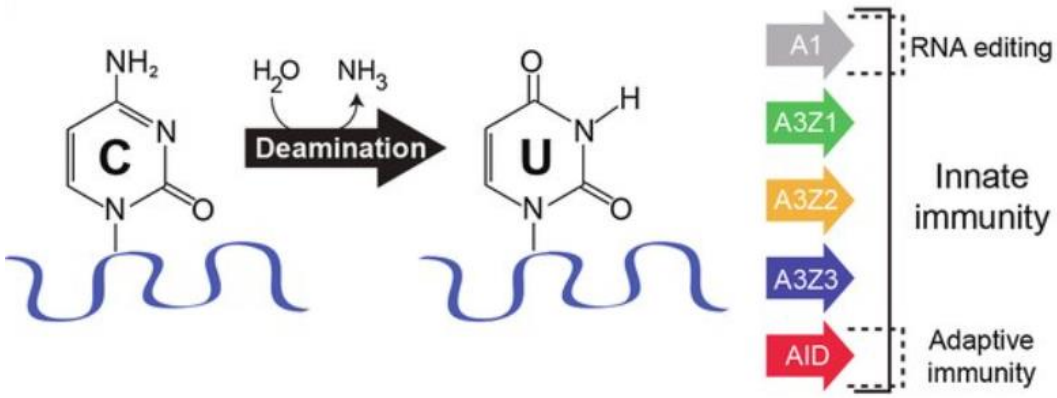
Mechanisms of innate immunity



IRGs – interferone regulated genes
Cytokines
Host-directed editing enzymes:
APOBEC, ADAR, AID..

APOBEC family members

- APOBEC ("apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like") is a family of evolutionarily conserved cytidine deaminases.
- Discovered due to their ability to eliminate HIV infection
- When misregulated, are a major source of mutation in numerous cancer types.
- AID is a part of adaptive immunity; it is responsible for hypermutation of variable immunoglobulin regions in lymphocytes



APOBEC1
APOBEC2
APOBEC3A
APOBEC3B
APOBEC3C
APOBEC3D
APOBEC3F
APOBEC3G
APOBEC3H
APOBEC4
AID (activation induced deaminase)

viruses

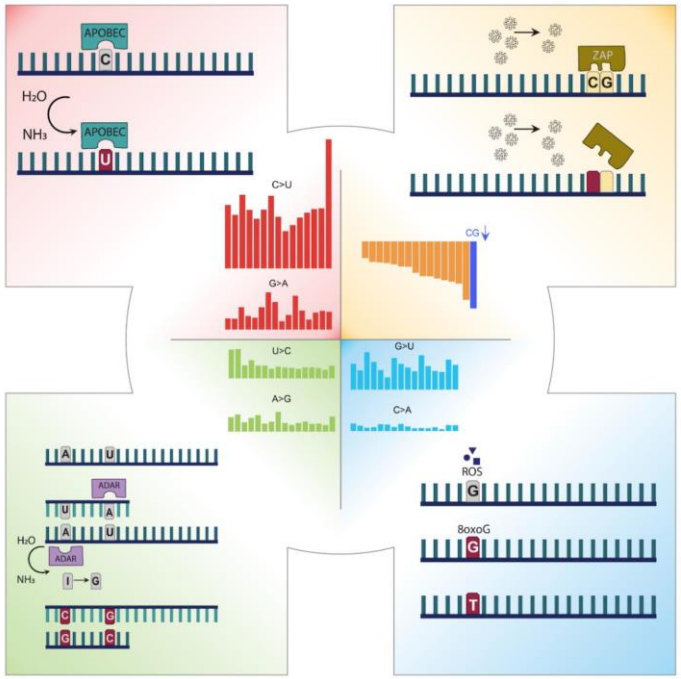
MDPI

Article

The Mutation Profile of SARS-CoV-2 Is Primarily Shaped by the Host Antiviral Defense

Cem Azgari, Zeynep Kilinc, Berk Turhan, Defne Circi and Ogun Adebali *

The results suggest that the heterogeneous mutation patterns are mainly reflections of host (i) antiviral mechanisms that are achieved through APOBEC, ADAR, and ZAP proteins, and (ii) probable adaptation against reactive oxygen species.



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Host-directed editing of the SARS-CoV-2 genome

Tobias Mourier [a, **, 1], Mukhtar Sadykov [a, 1], Michael J. Carr [b, c], Gabriel Gonzalez [b, c], William W. Hall [b, c, d], Arnab Pain [a, c, *]

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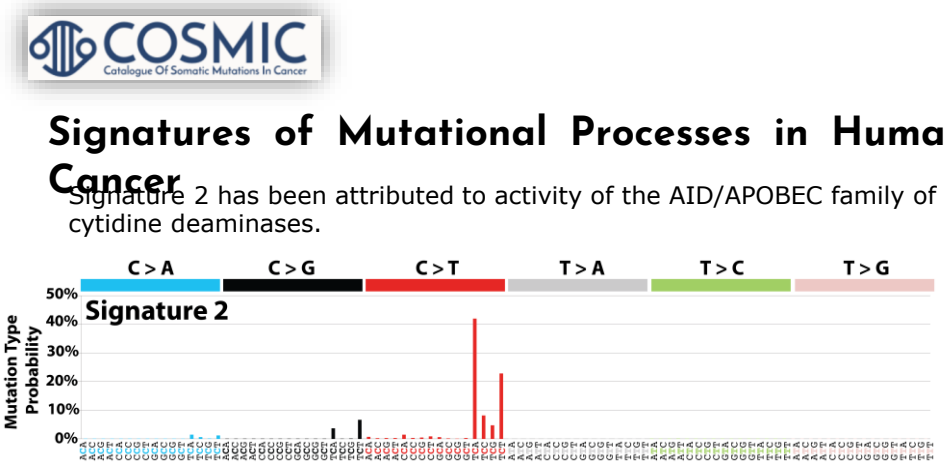
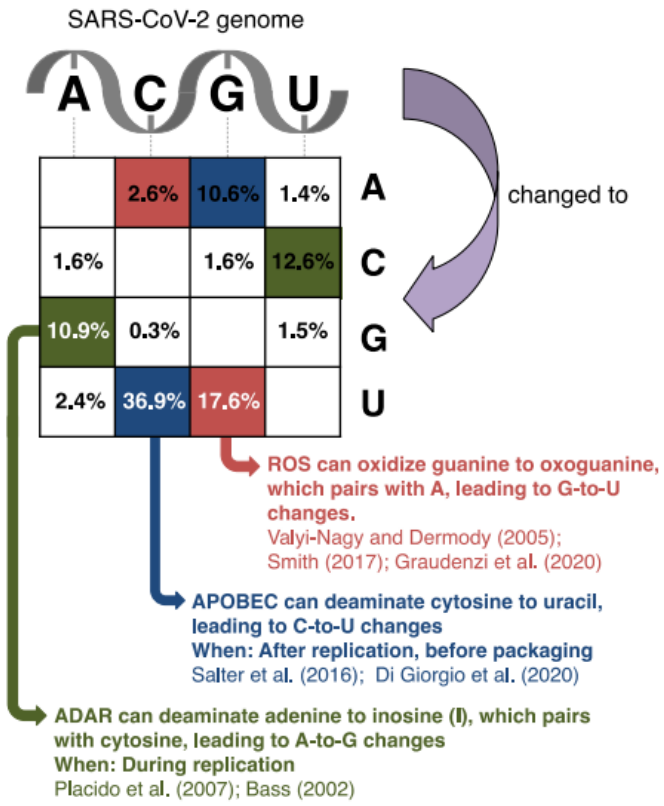
[c] Research Center for Zoonosis Control, Global Institution for Collaborative Research and Education (GI-CoRE), Hokkaido University, N20 W10 Kita-ku, Sapporo, 001-0020, Japan
[d] Global Virus Network (GVN), 801 W. Baltimore St., Baltimore, MD, 21201, USA





Article

578 | Nature | Vol 583 | 23 July 2020

Six reference-quality genomes reveal evolution of bat adaptations

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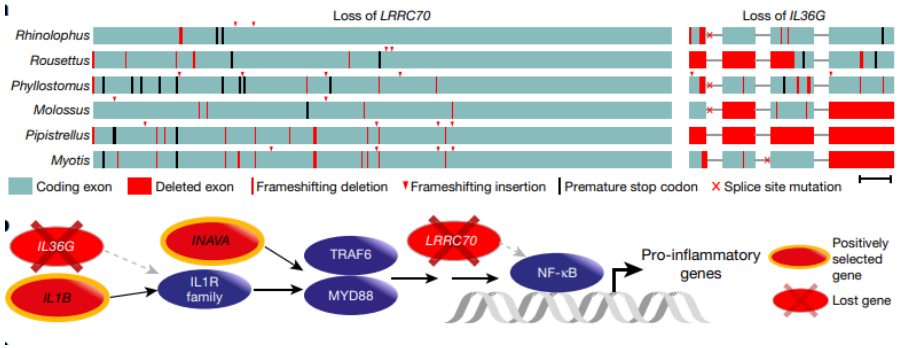
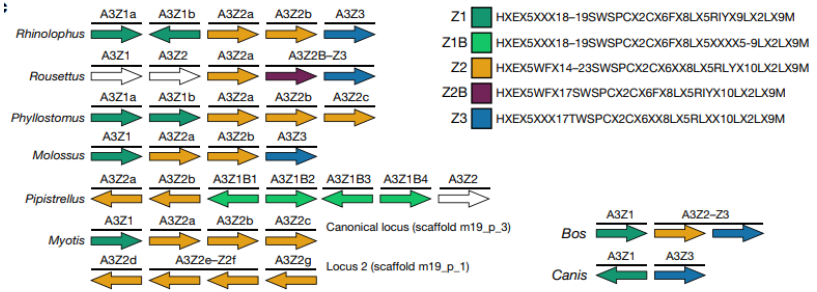
David Jebb[1,2,3,25], Zixia Huang[4,25], Martin Pippel[1,3,25], Graham M. Hughes[4], Ksenia Lavrichenko[5], Paolo Devanna[5], Sylke Winkler[1], Lars S. Jermiin[4,6,7], Emilia C. Skirmuntt[8], Aris Katzourakis[8], Lucy Burkitt-Gray[9], David A. Ray[10], Kevin A. M. Sullivan[10], Juliana G. Roscito[1,2,3], Bogdan M. Kirilenko[1,2,3], Liliana M. Dávalos[11,12], Angelique P. Corthals[13], Megan L. Power[4], Gareth Jones[14], Roger D. Ransome[14], Dina K. N. Dechmann[15,16,17], Andrea G. Locatelli[4], Sébastien J. Puechmaille[18,19], Olivier Fedrigo[20], Erich D. Jarvis[20,21,22], Michael Hiller[1,2,3,26]✉, Sonja C. Vernes[5,23,26]✉, Eugene W. Myers[1,3,24,26]✉ & Emma C. Teeling[4,26]✉

Loss of genes in NF-κB signalling pathway



Expansion of the APOBEC3 gene locus



https://twitter.com/bat1kgenomes?s=20