H.F.R.I.
Hellenic Foundation for Research & Innovation

PROJECT 01956/Evo.Res.Con.Edu

Unraveling the educational potential of the research and concepts of evolution

Biological evolution and Evolutionary Medicine

H.F.R.I. Hellenic Foundation for Research & Innovation
GSRI GENERAL SECRETARIAT FOR RESEARCH AND INNOVATION
UNIVERSITY OF IOANNINA
ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Υπουργείο Παιδείας, Θρησκευμάτων και Αθλητισμού

Biological evolution and Evolutionary Medicine

Direction 4: Holistic approaches based on evolutionary Theory in the context of wellness, disease, treatment, and biological death.

Introduction (1)
Some questions about the concepts of evolution

What is the ***Theory of evolution***?

(a) A theory about the origin of life?

(b) A theory that explains the similarities and differences between living organisms?

(c) A theory that explains the characteristics of life?

(d) A theory about the origin of humans?

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(b) Reproduction

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Why does evolution need ***genetic diversity***?

(a) Without genetic diversity, natural selection would be impossible to act

(b) A population with negligible genetic diversity would disappear and leave no offspring if the conditions of the environment became harsh

(c) A population with negligible genetic diversity would secure a very strong survival advantage under suitable environmental conditions

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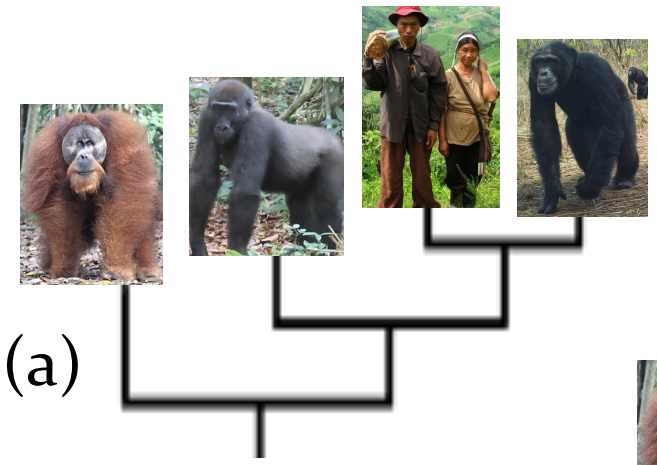
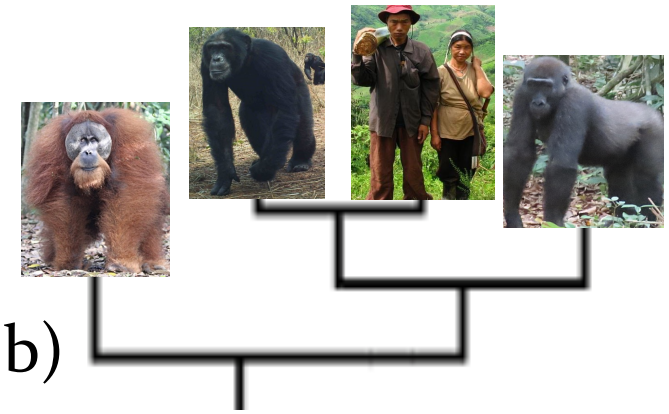
Introduction (2)
Some questions about the relevance of human to the concepts of evolution

Which of the following depictions can better outline the evolutionary trajectory of human?

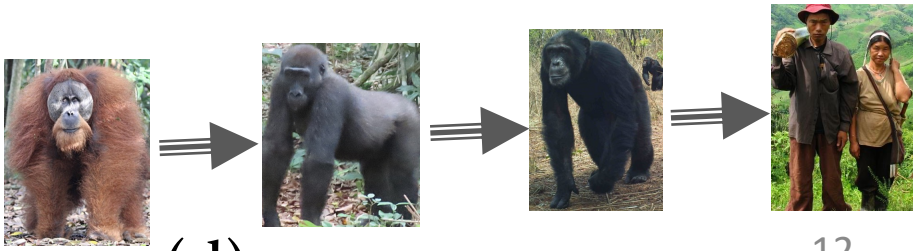


(a)



(b)

(c)



(d)

Sources of the icons for the species *Pongo abelii* (orangutan), *Gorilla gorilla*, *Pan troglodytes* (chimpanzee), *Homo sapiens*:
https://www.inaturalist.org/taxa/569678-Pongo-abelii
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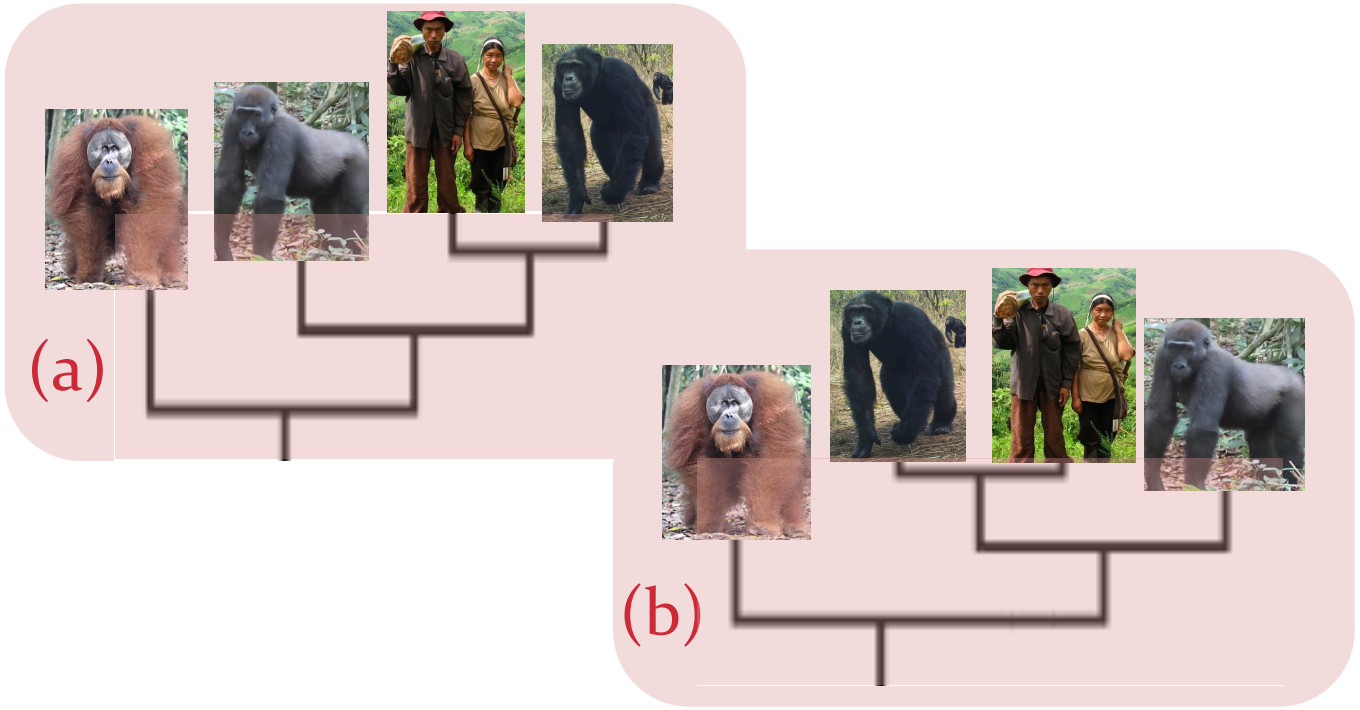

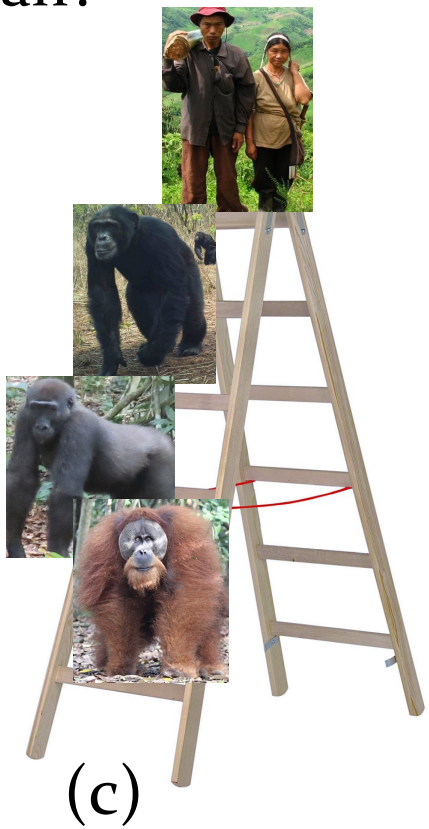

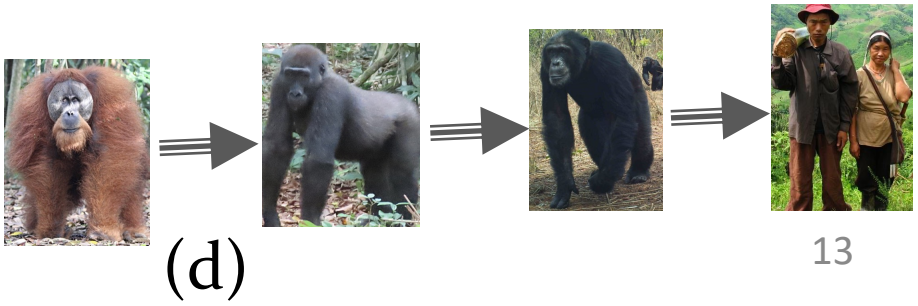

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Which of the following sentences is correct with respect to the ***evolutionary history of human*** on planet Earth?

(a) Human is the capstone of Creation

(b) Human is a species that evolved relatively recently on planet Earth

(c) The human species originated from the apes

(d) The human species has a long evolutionary history spanning millions of years on planet Earth

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What is the ***place of human*** *with relevance to the other organisms* that live on planet Earth?

(a) As it is true of all species, humans are dependent on other organisms with which they interact for survival and reproductive success

(b) Humans have developed unique (anthropogenic) environments in which they live without depending on other organisms for survival

(c) The human species has caused serious changes in the environment which impact the evolution of many other organisms on planet Earth

(d) The human species is evolving independent of the natural ecosystems which only matter to humans for touristic and recreational activities

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Why do ***human diseases*** exist in present-day world and why have they not been wiped out in the past due to ***natural selection***?

(a) Because these diseases are due to extrinsic factors and not to variations in the genetic material on which natural selection would effectively act

(b) Because the environments in which humans evolved in the past were different from the environments in which they live today

(c) Because many of these diseases appear late in life and their incidence is not affected by the reproductive success which is the true measure of natural selection

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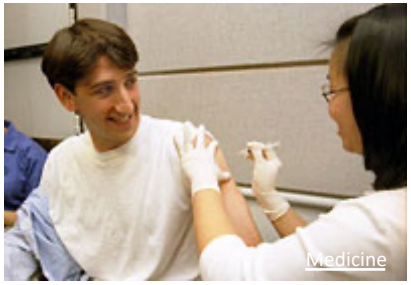
Why is evolution important for humans today?

Understanding evolution helps us resolve biological matters that affect our life.

- **Importance of change:** new possibilities but also chances for adaptation in an ever-changing world.
- **Agricultural economy:** improving the resistance of agricultural crops to parasitic diseases, reinforced by an understanding of evolutionary relationships and genetic diversity.
- **Sustainable development:** preventing extinction conditions and conserving biodiversity by applying policies that take into consideration the relationship between population size and genetic diversity.
- **Modern Medicine:** improvement of prognosis, diagnosis and treatment of diseases, owing to an understanding of the evolution of microorganisms and of genes connected to modern-day diseases.



Relevance of evolution

Source of images on the right: The relevance of evolution (UC Museum of Paleontology) https://evolution.berkeley.edu/the-relevance-of-evolution

Main theme (1)
Human genetic diversity relevance to evolution and human diseases

The human species has a relatively short but rich evolutionary history.

Microorganisms (bacteria) emerged 3.7 to 4 billion years ago. Photosynthesis evolved 2.7 to 3 billion years ago. Eukaryotic microorganisms appeared 2 billion years ago. Multicellular organization emerged 1 billion years ago. Vertebrates emerged 0.5 billion years ago. Humans (*Homo sapiens*) are only 200 to 300 thousand years old.

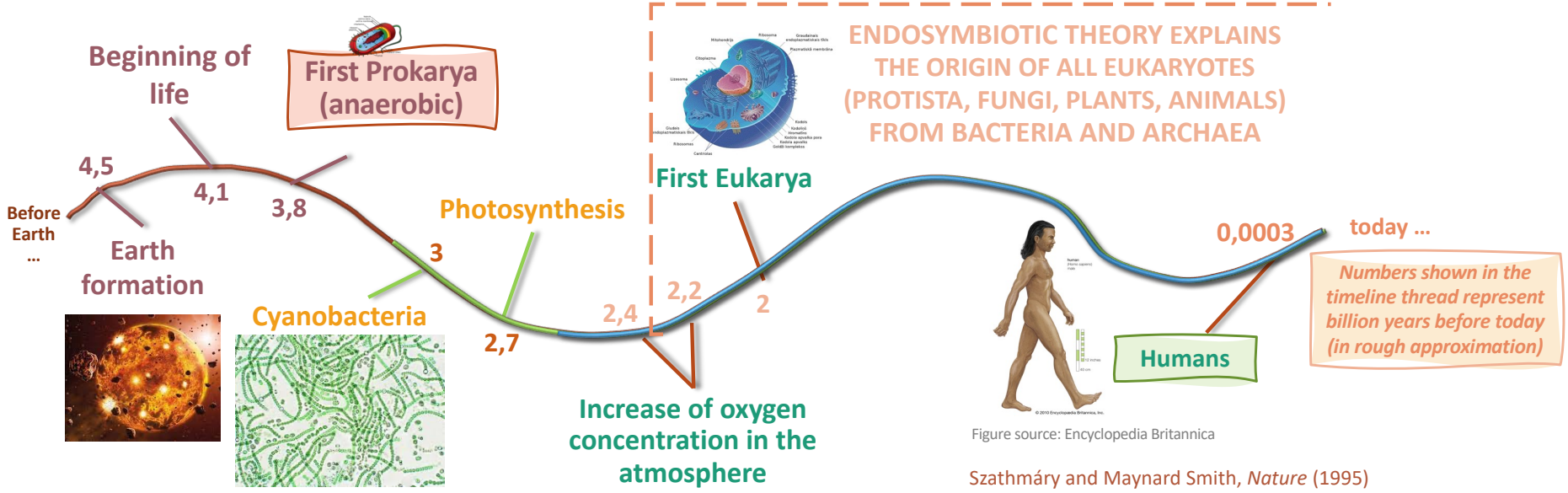


Figure source: Encyclopedia Britannica

Szathmáry and Maynard Smith, *Nature* (1995)

The human species has a relatively short but rich evolutionary history.

Some of our now-extinct relatives have lived longer than us on planet Earth (*Homo erectus*, *Homo naledi*, *Homo ergaster, Homo habilis*, etc.).

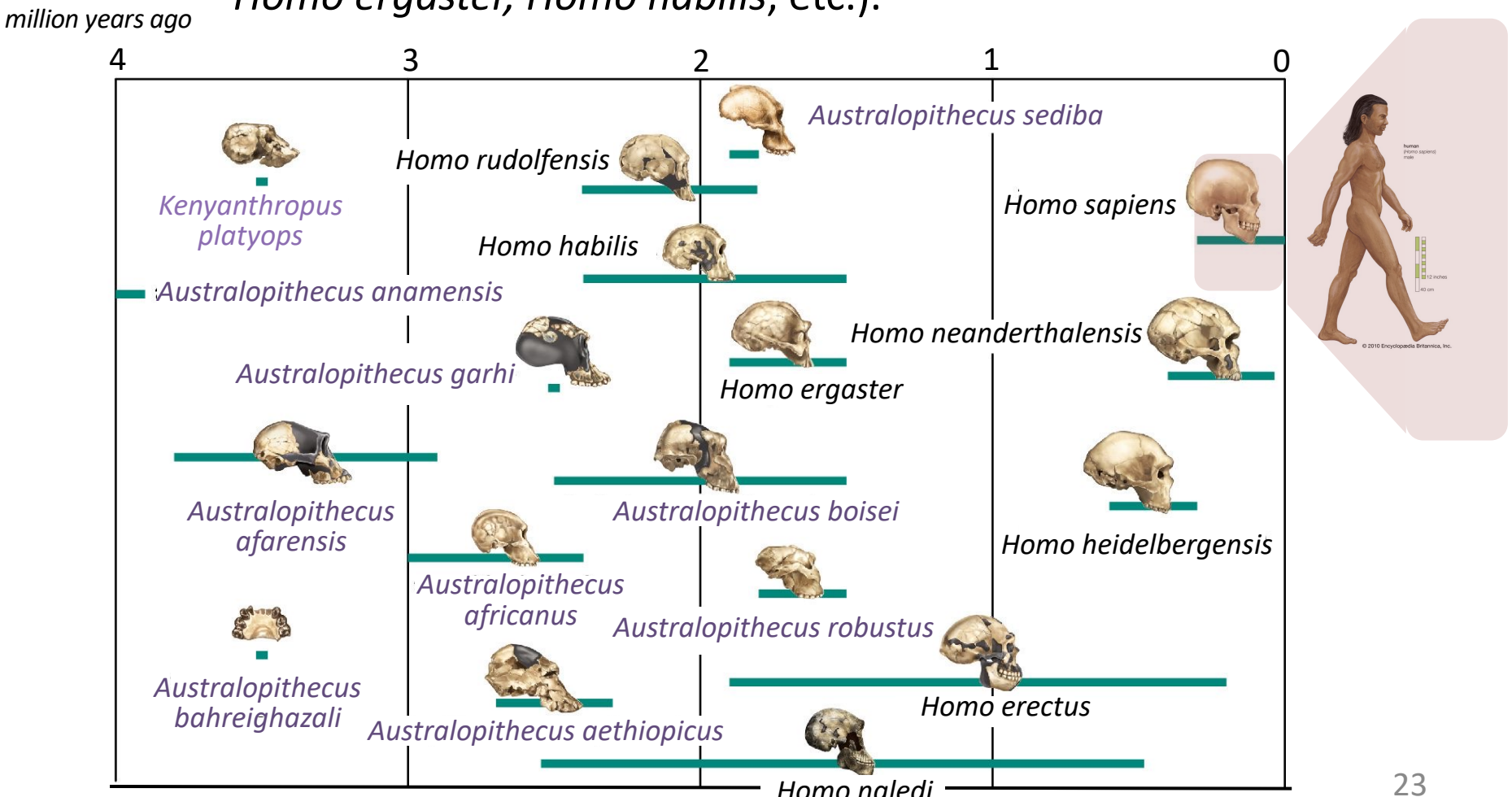
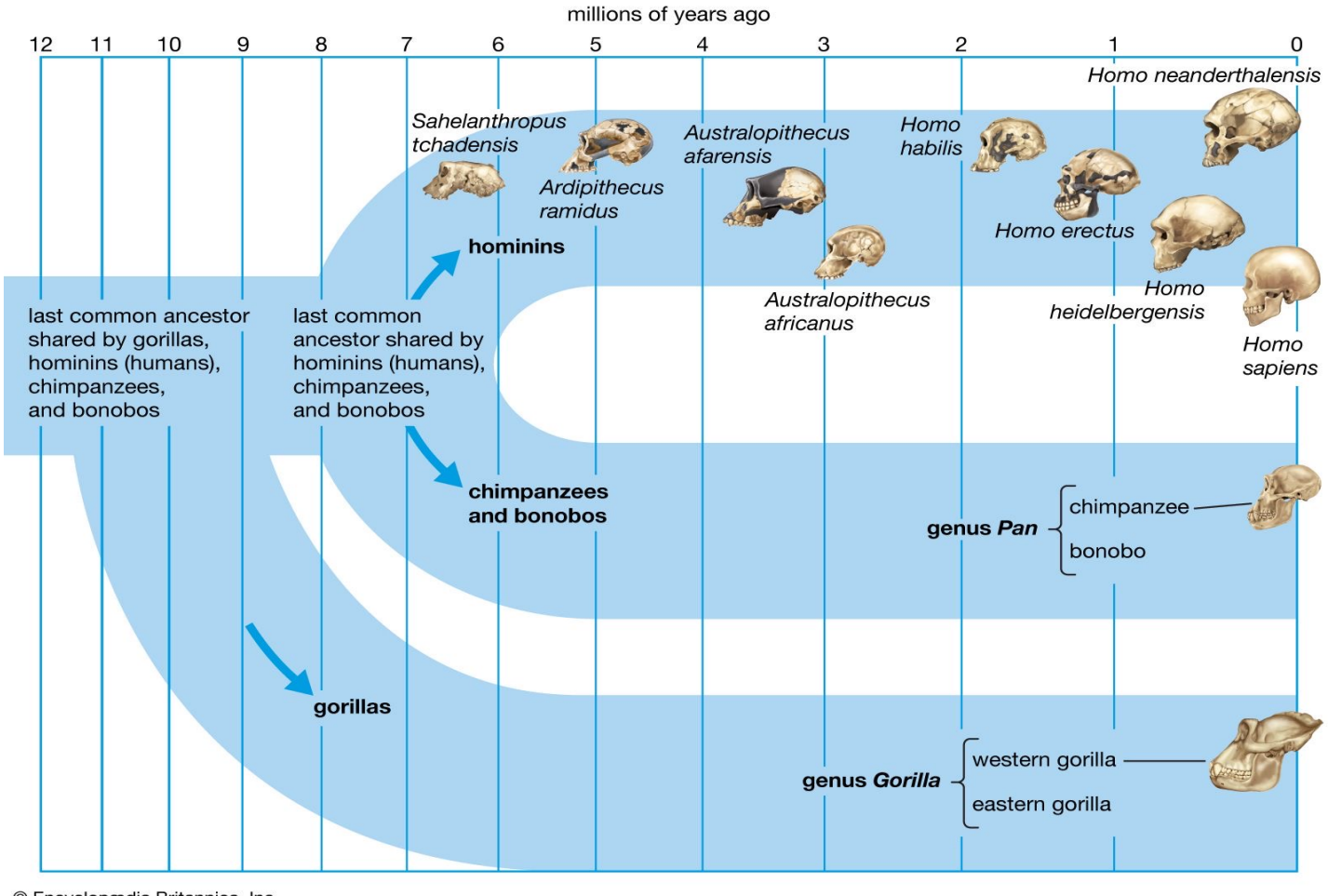


Figure source: Encyclopedia Britannica

The human species has a relatively short but rich evolutionary history.

Our closest extant relatives today (chimpanzee, bonobo) have evolved from the same common ancestor but in a distinct evolutionary "line" for at least 6-7 million years. Are we a "brotherless" species?



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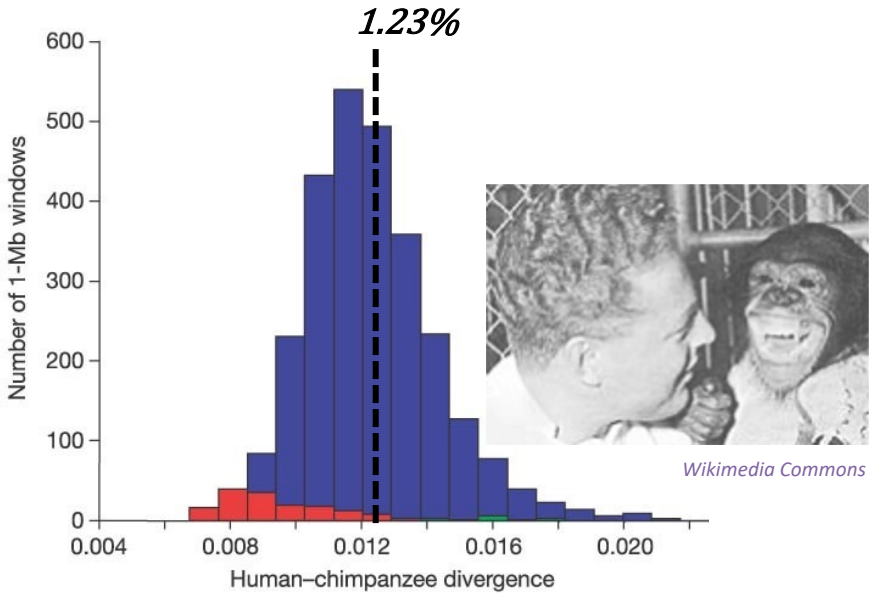
The **similarity** of our genome with the genomes of chimpanzee and bonobo is **strikingly high**. The genomes of human and chimpanzee are of similar size and contain roughly the same number of genes and essentially equivalent number of chromosomes, while they differ in only 5% of the genes and 1.23% of single nucleotide polymorphisms (SNP), and 30% of human genes encode identical protein sequences as the homologous chimpanzee genes!



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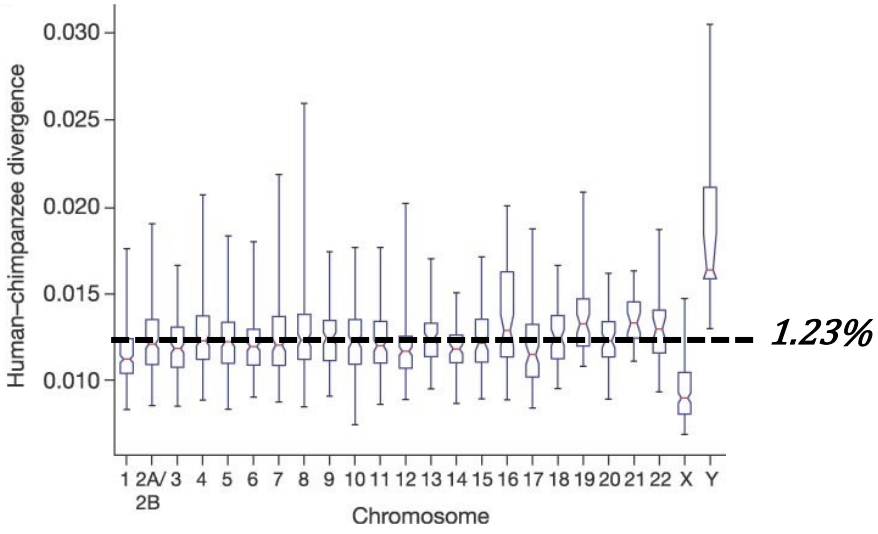

The Chimpanzee Sequencing Analysis Consortium, *Nature* 437: 69-87 (2005)
Initial sequence of the chimpanzee genome and comparison with the human genome.

The human species has a relatively short but rich evolutionary history.

Are they really such few DNA differences between human and chimpanzee?

- Differences are 1.2% based on single-nucleotide sites (35 x10^6 SNPs), but 4% if we also consider large DNA insertions and deletions (which imply recent transposition events).
- 10% of the SNP differences (**3 x10^6 SNPs**) are in genes, being relevant to unique human characteristics and susceptibility to diseases such as Alzheimer's, HIV/AIDS, cancers.
- 5% of the human genes (about 1000 genes) are quite different (the remaining 95% differ only slightly in gene product (protein) sequence from their counterparts in chimpanzee).
- Some of the human genes (> 50) are absent from the chimpanzee genome, including genes that are relevant to the immune system and inflammatory response reactions.
- Some human genes have undergone rapid changes (**Human Accelerated Regions**_HAR): those encode transcription factors or small regulatory RNAs important in embryogenesis.
- Some genetic loci (> 7) seem to have accumulated very rapid changes (**selective sweeps**) during the last 500 thousand years: these genetic loci contain genetic elements that are involved in regulation of nervous system development, genes associated with evolution of the human speech (*FOXP2*) but also genes for susceptibility to cystic fibrosis (*CFTR*).

The Chimpanzee Sequencing Analysis Consortium, *Nature* 437: 69-87 (2005)
Initial sequence of the chimpanzee genome and comparison with the human genome

Vakri and Altheide, *Genome Res.* (2005)
Comparing the human and chimpanzee genomes: searching for needles in a haystack

The human species has a relatively short but rich evolutionary history.

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- During the last 7 million years, our ancestors have developed specializations such as ***bipedalism***, ***speech***, and ***triplication of the cerebral cortex size***. Many of these characteristics derive from changes in the **cellular behavior during ontogenetic development** which, in turn, reflect **changes in molecular regulatory networks** that have been modified in a relatively short time scale in the hominin evolution.

- The **few genes that differ** largely in human relative to chimpanzee include **genes with important roles** in the development of **nervous system** (regulatory RNA, transcription factors) leading to extensive differences in the patterns of gene expression and gene product interactions ***important for brain development*** during embryonic and early postembryonic life.

The Chimpanzee Sequencing Analysis Consortium, *Nature* 437: 69-87 (2005)
Initial sequence of the chimpanzee genome and comparison with the human genome

She *et al.*, *Cell* (2023)
Comparative landscape of genetic dependencies in human and chimpanzee stem cells

The human species has a relatively short but rich evolutionary history.

As it is true of all species, the history of our genetic diversity is being documented in our genomes.

The human genetic material contains genes of various ages:

1,5 to 4 billion years [basal metabolic pathways]

1,5 to 2,5 billion years [eukaryotic, chromosomes, sex],

1 billion years [ontogenesis, multicellularity],

500 million years [immune system, adaptive immunity],

230 million years [endothermy, lactation],

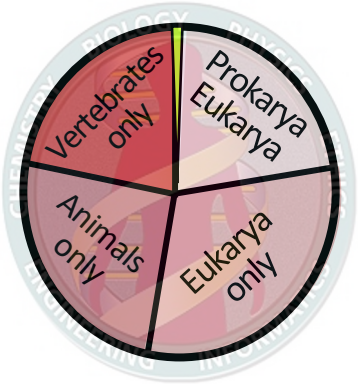
190 million years [placenta],

15 million years [invasive placenta],

7 million years [bipedalism],

5 million years [short periods between childbirths],

2-3 million years [dark skin color] etc.

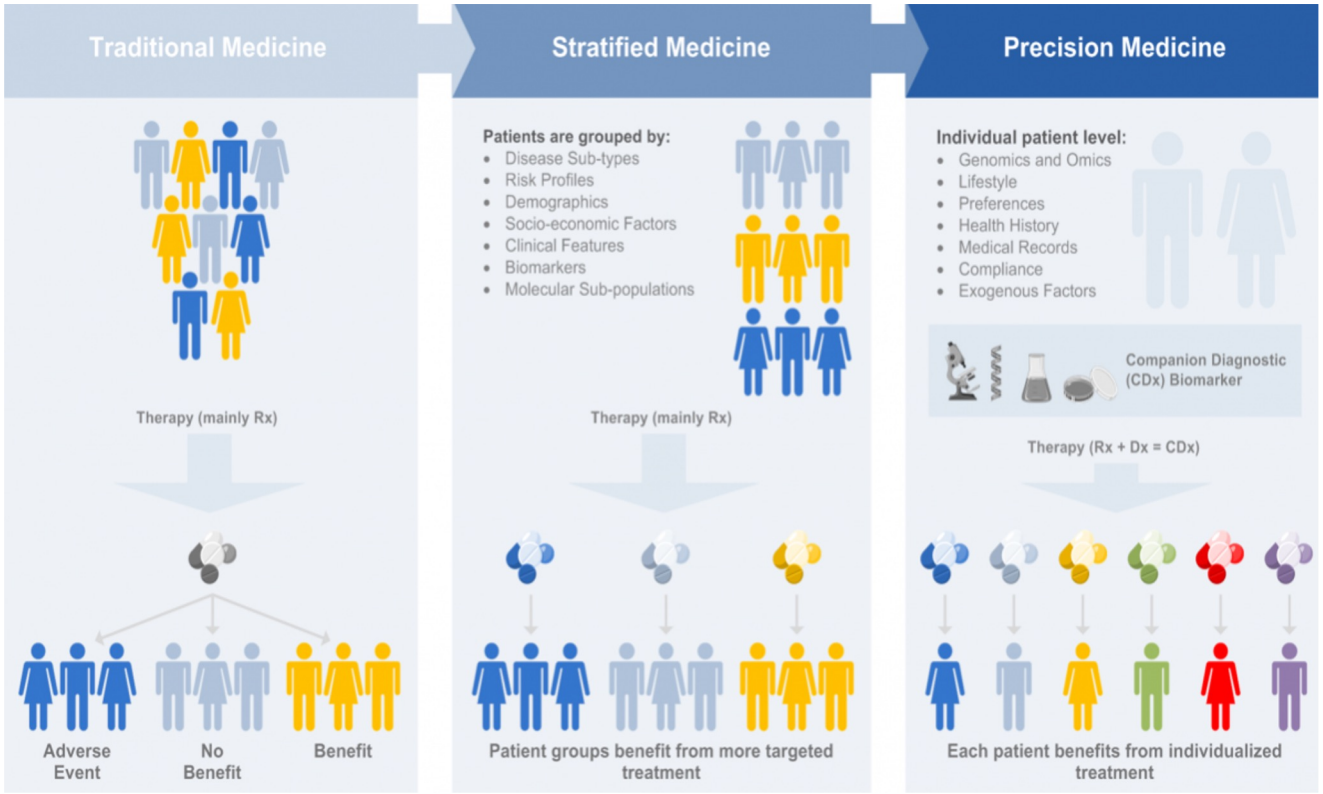


The 20 thousand genes of the human genome are kin to other genes in various ranges of species, indicative of their **evolutionary age**!

The Human Genome Sequencing Consortium, *Nature* 409: 860-921 (2001); Fig. 38 (στα δεξιά)

The human species has a relatively short but rich evolutionary history.

The analysis of genetic diversity through the study of our genomes helps us understand our evolutionary history and the differences among human populations in an evolutionary perspective. It also offers us a base for better understanding of human diseases and potential design of precision medicine interventions.

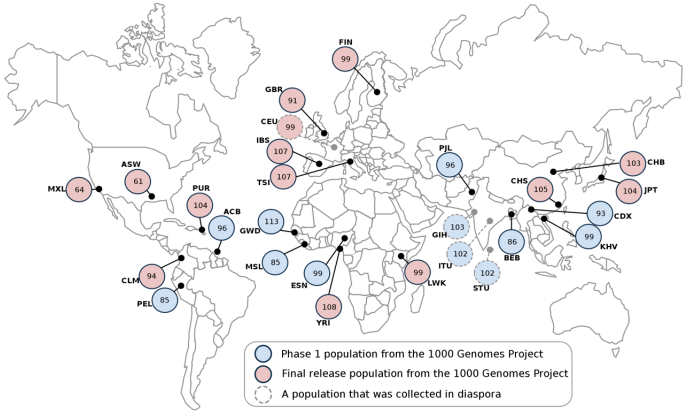


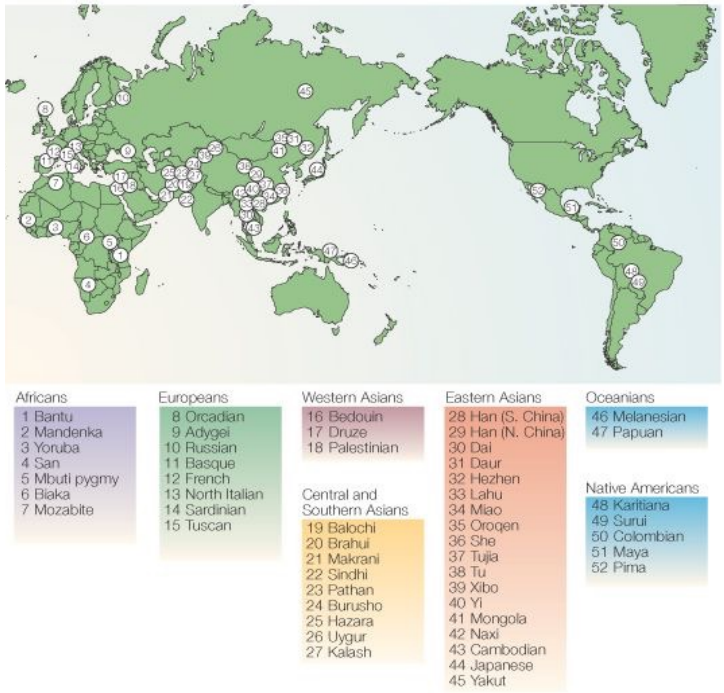
Hays, Introduction (Fig. 1.3), In: *Advancing Healthcare Through Personalized Medicine* (2021)

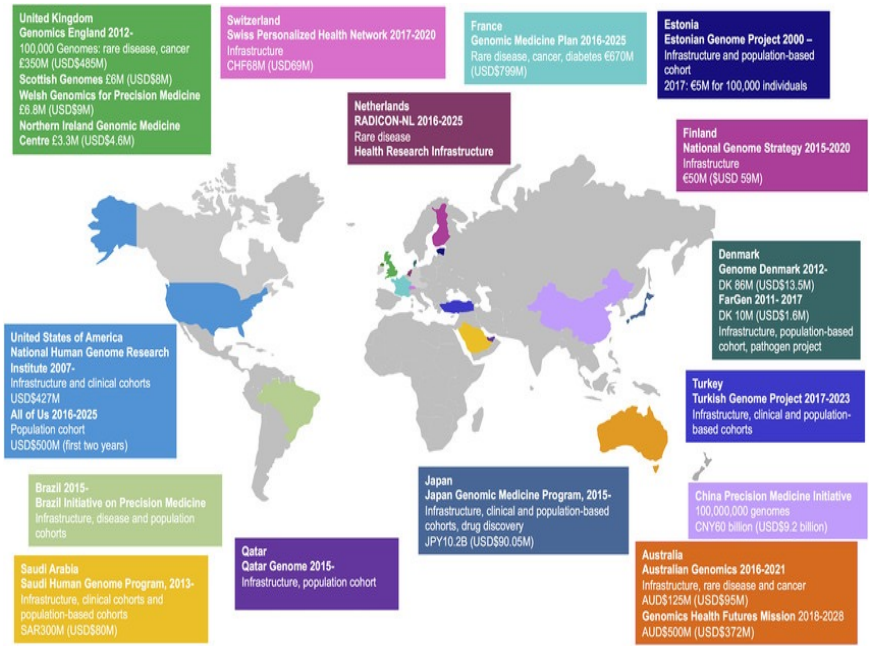
The human species has a relatively short but rich evolutionary history.

What can we learn from the analysis of our genomes?

HapMap project (2002-2010)
Human Genome Diversity project
1000 Genomes project
Genome of Europe project etc.







L. Luca Cavalli-Sforza, *Nature Rev. Genet*. 6: 333-340 (2005)
The Human Genome Diversity Project: past, present and future.

The human species has a relatively short but rich evolutionary history.

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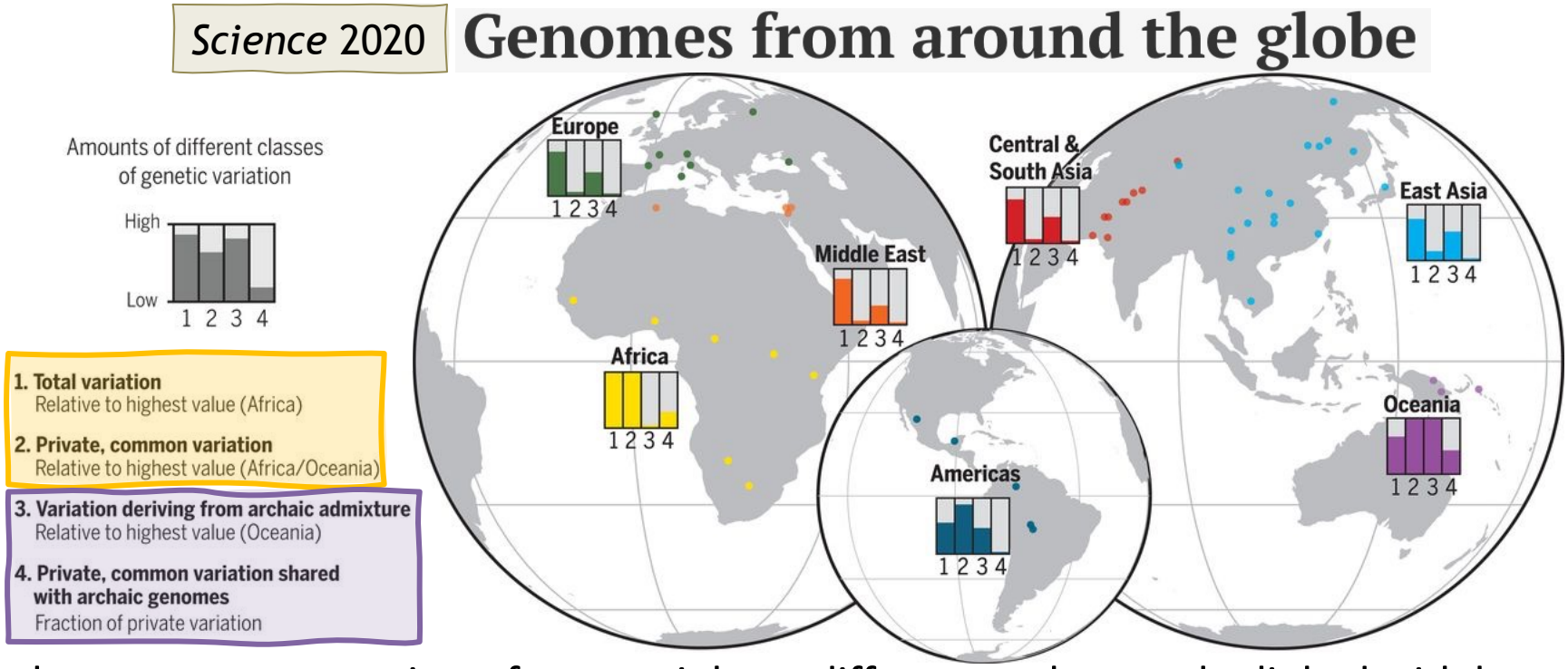
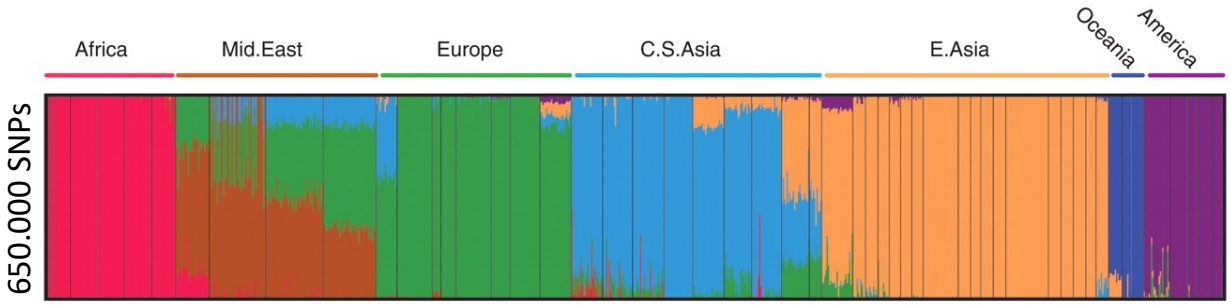


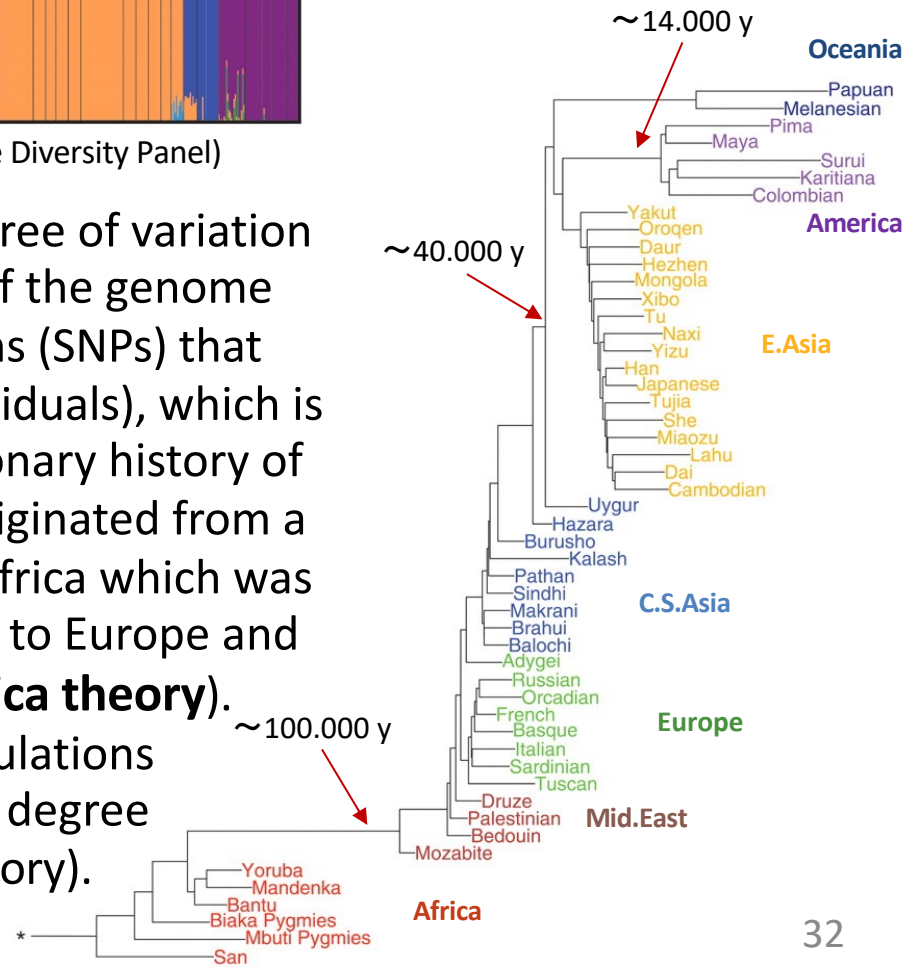
The human genome projects focus mainly on differences that can be linked with human diseases or differences that provide clues for the evolutionary history of genetic diversity. The Human Genome Diversity (HGD) Project (see Figure) provided clear evidence that populations native to Africa show the highest degree of in-population diversity among all human populations and populations native to Oceania show the highest degree of archaic admixture (from Denisovan) in their genomes. Source: Bergström *et al.*, *Science* 367: eaay5012 (2020); Graphical abstract.

Human genetic diversity evolved first in Africa and then out of Africa.



938 human genomes from 51 populations (Human Genome Diversity Panel)

Human genomes show a rather limited degree of variation between each other (for example, < 0.1% of the genome represents single-nucleotide polymorphisms (SNPs) that differ at significant frequencies among individuals), which is consistent with the relatively short evolutionary history of *Homo sapiens* (200-300 thousand years) originated from a rather homogeneous initial population in Africa which was then followed by migrations of populations to Europe and Asia (< 100 thousand years ago) (**Out of Africa theory**). The diversity in the present-day native populations around the globe reflects evolution (higher degree of variation signifies longer evolutionary history).



Li *et al.*, *Science* 319: 1100-1104 (2008)
Worldwide human relationships inferred from genome-wide patterns of variation.

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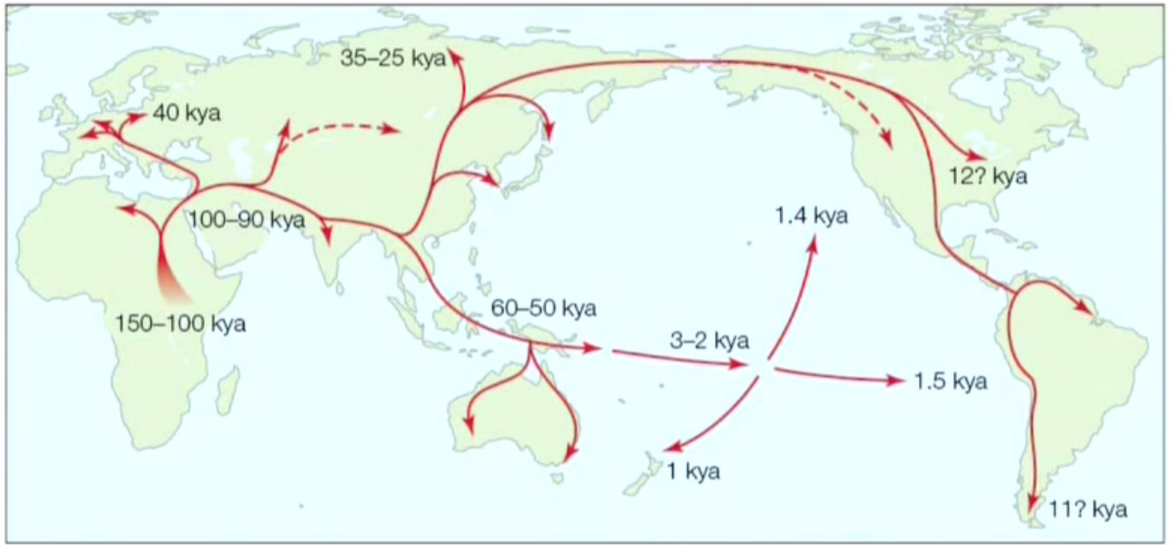
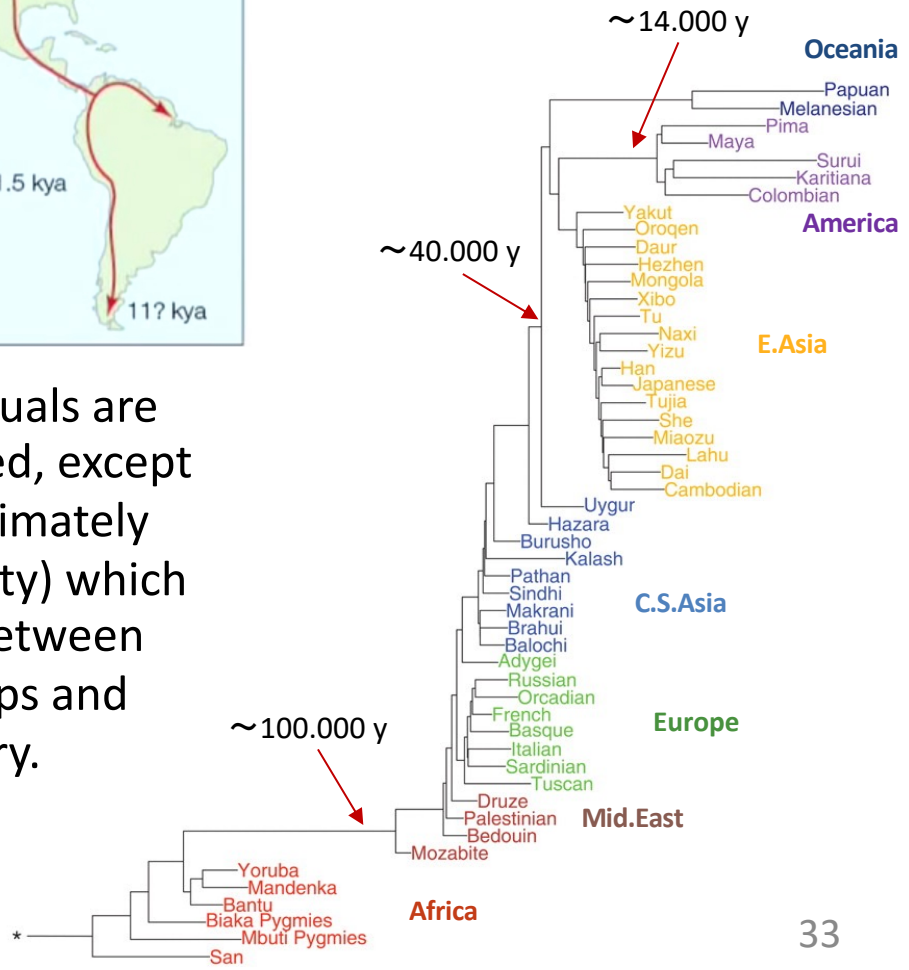


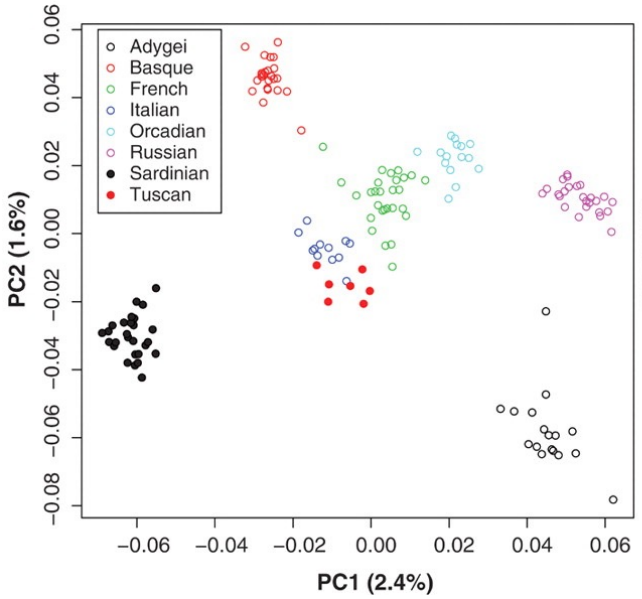
In total, similar differences between individuals are widespread in all human populations studied, except for relatively few sites (< 10% of the approximately 300,000 SNPs that show significant variability) which can be used as markers for distinguishing between different populational or geographical groups and provide clues for human evolutionary history.



Li *et al.*, *Science* 319: 1100-1104 (2008)
Worldwide human relationships inferred from genome-wide patterns of variation.

Most of human genetic diversity is common in all human populations.

Markers	Sites (number)	Percentage of genetic diversity (%) in the same population	among (>50) populations	among (5-7) groups	
DNA	109	84.4	4.7	10.8	(1997)
CNVs	783	94.0	2.3	3.7	(2005)
SNPs	650.000	88.9	2.1	9.0	(2008)
X-SNPs	~30.000	84.7	2.4	12.9	(2008)
X-CNVs	20	90.4	4.6	4.9	(2004)



How would it be possible to distinguish between different geographical or other groups of human populations that we suppose to include important variations? Differences in diversity, independent of the genetic marker used, are rather limited. All studies show that the genetic variation differences are much greater between individuals of the same population than between different populations (five relevant studies are summarized in the Table).

Normally, for identification of such differences, scientists use genetic markers corresponding to only a small proportion (not more than 4-5%) of the total genetic diversity. A relevant example (from HGD Project) is shown in the Figure.

Barbujani and Colonna, *Trends Genet*. 26: 285-295 (2010)
Human genome diversity: frequently asked questions.

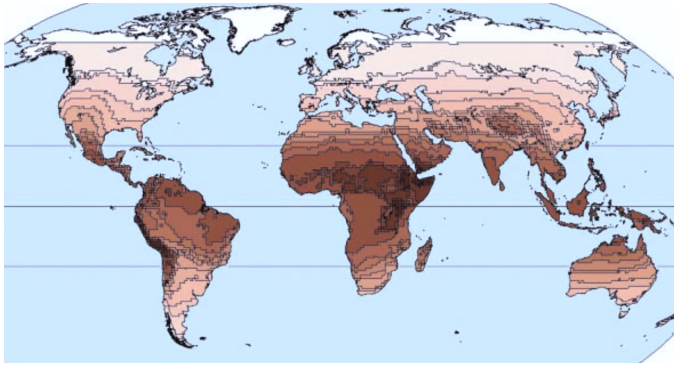
Differences in traits like the color of the skin reflect only a minor part of human genetic diversity.

Dark skin color evolved as a common feature in our ancestors almost 2 million years ago, well before the appearance of *Homo sapiens*. Dark color offers protection to the bare skin (which also was an important innovation at the time, allowing sweating during intense movement) from ultraviolet radiation (UV).

Reconstruction of early *Homo erectus* from Africa by paleontologist paleoartist Mauricio Antón (see N. Jablonski (2012) *Proc. Am. Phil. Soc.* 156, 45-57 and The Leaky Foundation (2018) N. Jablonski Lecture on *Evolution and meanings of human skin color*)

After dispersal of *Homo sapiens* out of Africa (< 100 thousands of years and more recently) and in colder areas, the known geographical distribution in light and dark color grades began gradually to appear. Adaptation to environments exposed to low-intensity UV is linked with **reduced melanin production** which allows more effective utilization of UV in the vitamin D synthesis pathway. Thus, the reduced melanin production offers an evolutionary tradeoff between the UV harmful effect on reproduction and its benefit for vitamin D synthesis.

Source: Jablonski, *Pigment Cell Melanoma Res.* (2021)

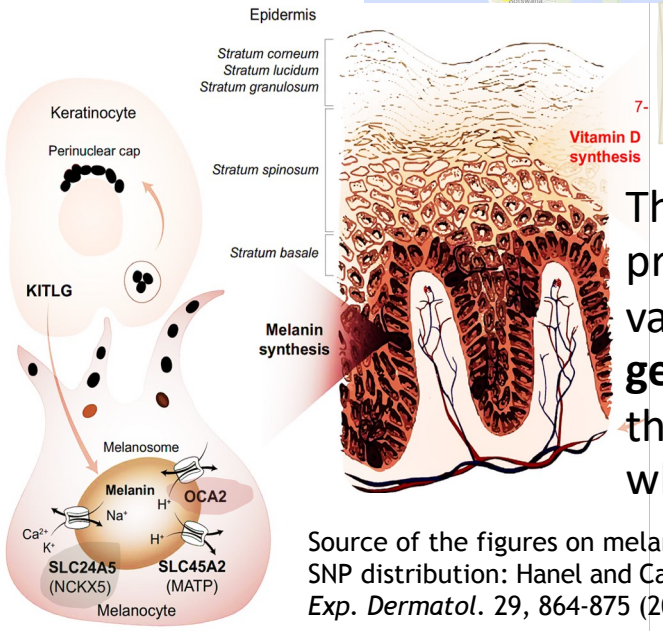


Source: Fig. 3 from article: Chaplin (2004) *Am. J. Phys. Anthropol.* 125, 292-302.

Differences in traits like the color of the skin reflect only a minor part of human genetic diversity.

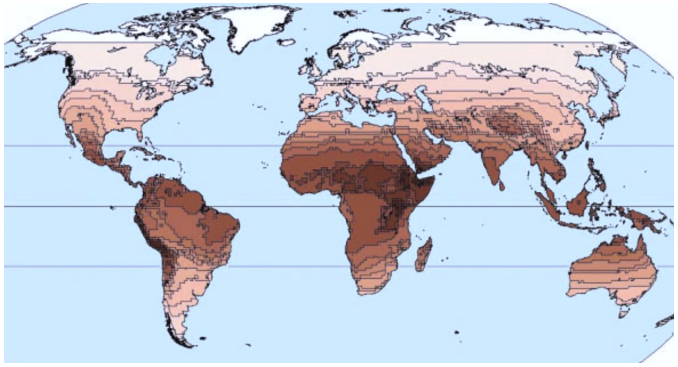
A variant (SNP) of the *SLC24A5* gene is associated with 25-40% of the color difference between Europe and African native populations.

A variant (SNP) of the *OCA2* gene is associated with 8-10% of the color difference between East Asian and African native populations.



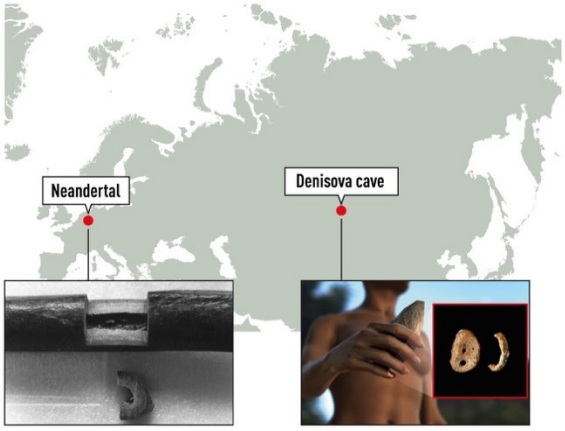
The differences in melanin production are related to variations in **some important genes**, like permease genes that control melanosome pH which is crucial for function of a key enzyme in melanin synthesis.

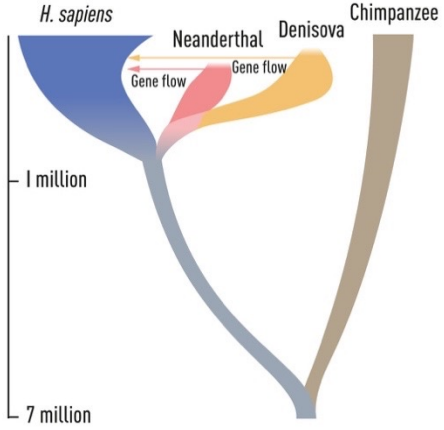
Source of the figures on melanin and SNP distribution: Hanel and Carlberg, *Exp. Dermatol.* 29, 864-875 (2020)

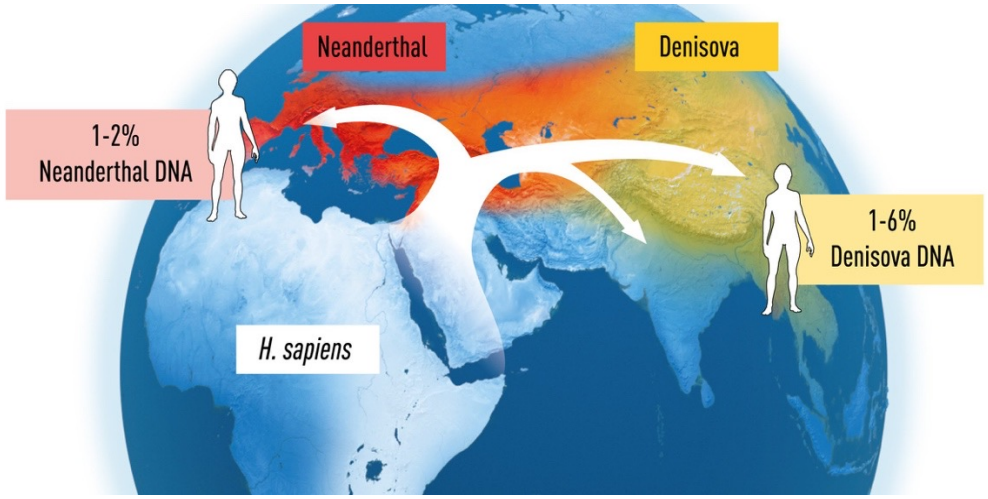


Source: Fig. 3 from article: Chaplin (2004) *Am. J. Phys. Anthropol.* 125, 292-302.

The human genomes contain genes that have been transferred from Neanderthal or Denisovans.



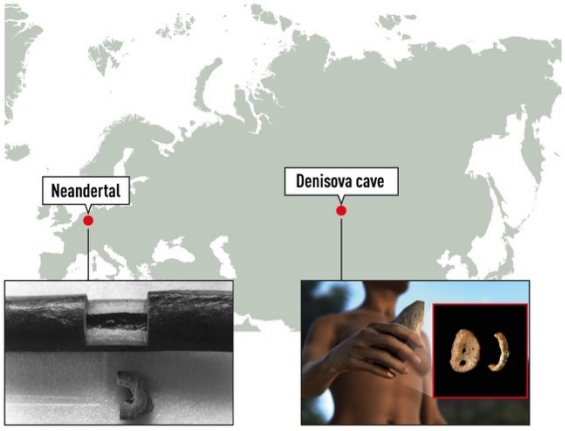


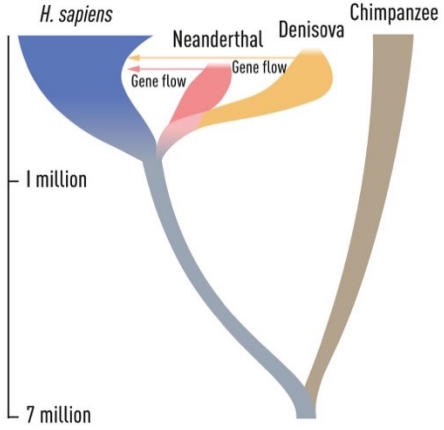


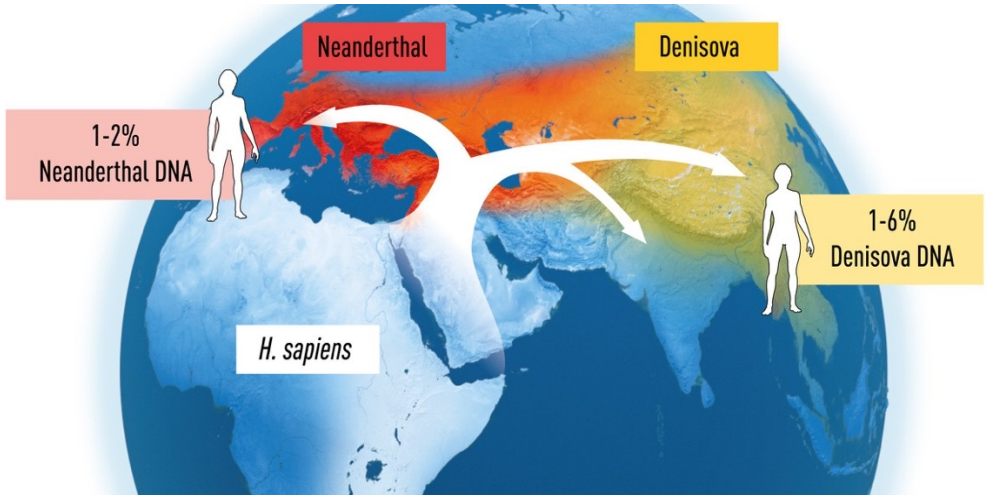
Source: The Nobel Prize in Physiology and Medicine 2022 Press Release
https://www.nobelprize.org/prizes/medicine/2022/press-release/

The research of Svante Pääbo (Nobel Prize 2022) introduced the field of ***paleogenomics*** to the study of human evolutionary history. Capitalizing on discoveries from excavations at the sites Neandertal and Denisova cave, the Pääbo research team isolated and analyzed archaic DNA of human relatives that are now extinct and showed that DNA of **Neanderthals** and **Denisovans** is present to a significant extent in present-day genomes of *Homo sapiens*, mostly in genomes of European and East Asian or Oceanian origin, respectively.

The human genomes contain genes that have been transferred from Neanderthal or Denisovans.







The findings of Svante Pääbo **imply** the occurrence of *gene transfer* (**gene flow**) from Neanderthal and Denisovan genomes to our species (*Homo sapiens*) that had happened in the period of approximately 70 to 30 thousand years ago, **after** the dispersal of humans out of Africa. Some of the transferred genes were linked to adaptations of metabolism or the immune system that are still important for humans today.

Source: The Nobel Prize in Physiology and Medicine 2022 Press Release
https://www.nobelprize.org/prizes/medicine/2022/press-release/

Racimo *et al.*, *Mol Biol Evol* 34: 296-317 (2017)
Signatures of archaic adaptive introgression in present-day human populations.

Human genes that allow resistance to cold have been derived from Denisovans.

What the figure shows:
Geographical distribution of the frequency of an **allele** of genetic locus *TBX15*/*WARS2* that affects expression of these genes and is related to adaptation to cold climates. This allele is mostly prevalent in Greenland Inuit people but also found in populations of America and Eurasia and is considered to have been derived, through gene flow, from the genomes of Denisovan.

Inuit of Greenland

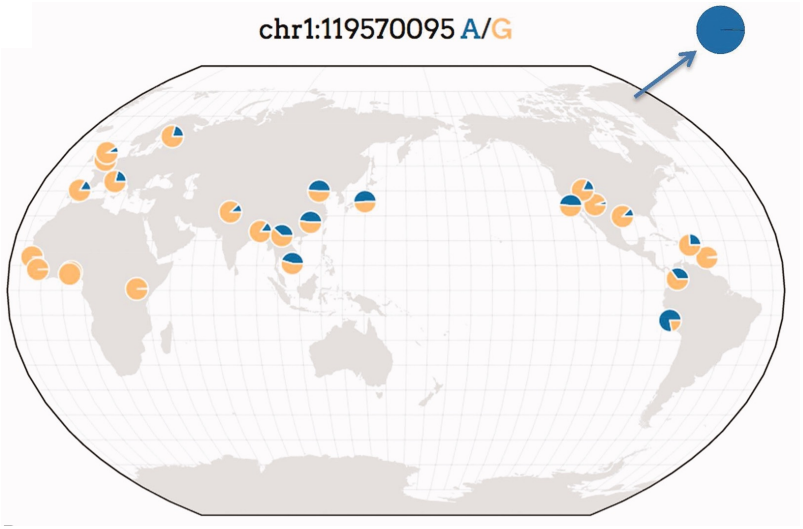


Figure source: Racimo *et al.* (2017) *Mol. Biol. Evol.* 34, 509-524; Fig. 1A

Several human genes that have been derived with introgression from Neanderthal or Denisovans are important in immune reaction, in metabolic adaptations to cold or high altitude, or are associated with skin color or with the nervous system and the musculoskeletal system. Inuit people of Greenland possess alleles at the genetic locus of two genes that are linked with adipose tissue differentiation and body fat distribution. These alleles have been derived from Denisovans and represent adaptations to cold.

Racimo *et al.*, *Mol Biol Evol* 34: 509-524 (2017)
Archaic adaptive introgression in *TBX15*/*WARS2*.

A susceptibility mutation to type 2 diabetes has been derived from Neanderthal.

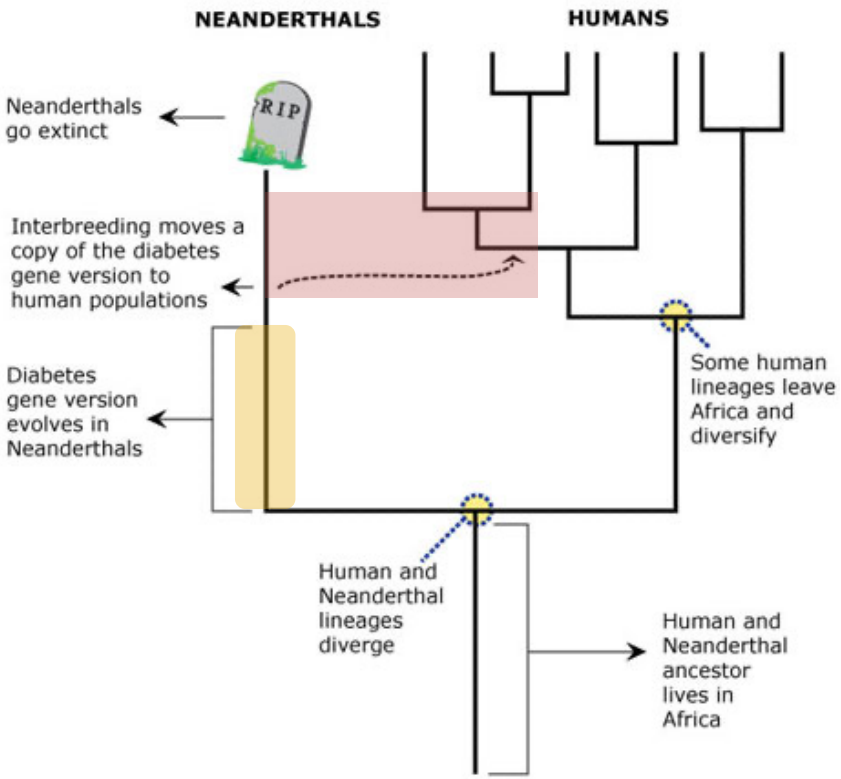


Figure source: Understanding Evolution "The deep roots of diabetes" https://evolution.berkeley.edu/evo-news/the-deep-roots-of-diabetes/

Several human genes that have been derived with introgression from Neanderthal or Denisovans are important in immune reaction, in metabolic adaptations to cold or high altitude, or are associated with skin color or with the nervous system and the musculoskeletal system. The descendants of native Americans in Mexico possess an allele of gene *SLC16A11* that causes deficient lipid transport to liver cells and has been linked with very high susceptibility to type 2 diabetes. This allele has been derived through gene transfer from Neanderthals.

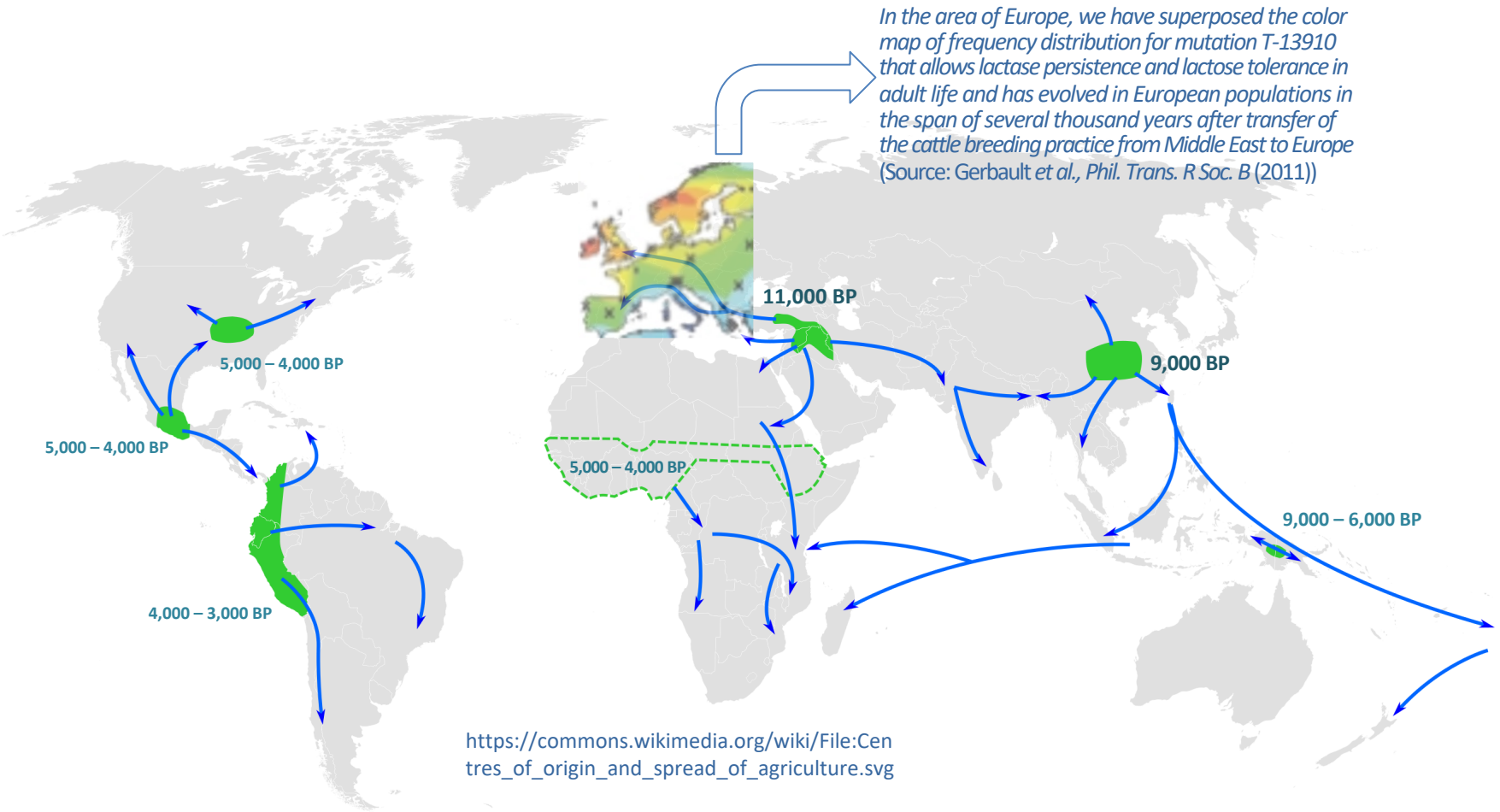
SIGMA Type 2 Diabetes Consortium, *Nature* 506: 97-101 (2013) Sequence variants in SLC16A11 are a common risk factor for type 2 diabetes in Mexico.

Main theme (2)
Human impact on the environment and evolutionary mismatch diseases

Humans impact the environment and the evolution of other organisms.

In the relatively recent human evolutionary history, we recognize **two major transitions in the lifestyle** of *Homo sapiens*, which had serious impacts on the environment and on other organisms, as well as on human themselves. These are the **Neolithic** (or **Agricultural**) Revolution (the transition from a nomadic hunter-gatherer lifestyle to a farmer-herder lifestyle established in permanent settings, which created the foundation for the recent transition to industrialization) and the **Urban** (or **Industrial**) Revolution (mechanization of agriculture and secondary production; revolution in the use of power; demographic, epidemiologic and ecological transitions; impact on biodiversity, climate, health, social network). The impacts are complex, both on human environment and other organisms, and on human themselves.

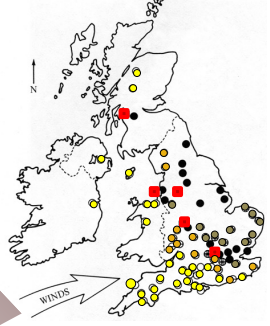
Neolithic-agricultural epoch



Sites and approximate dates of birth of Neolithic (Agricultural) Revolution

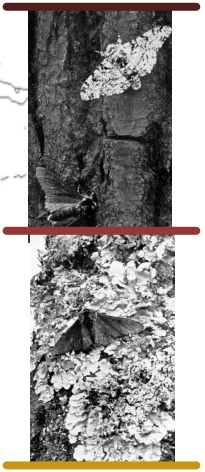
Initial source of the figure:
Science 300, 597-603 (2003)
Farmers and their languages:
The first expansions. (Fig. 1)

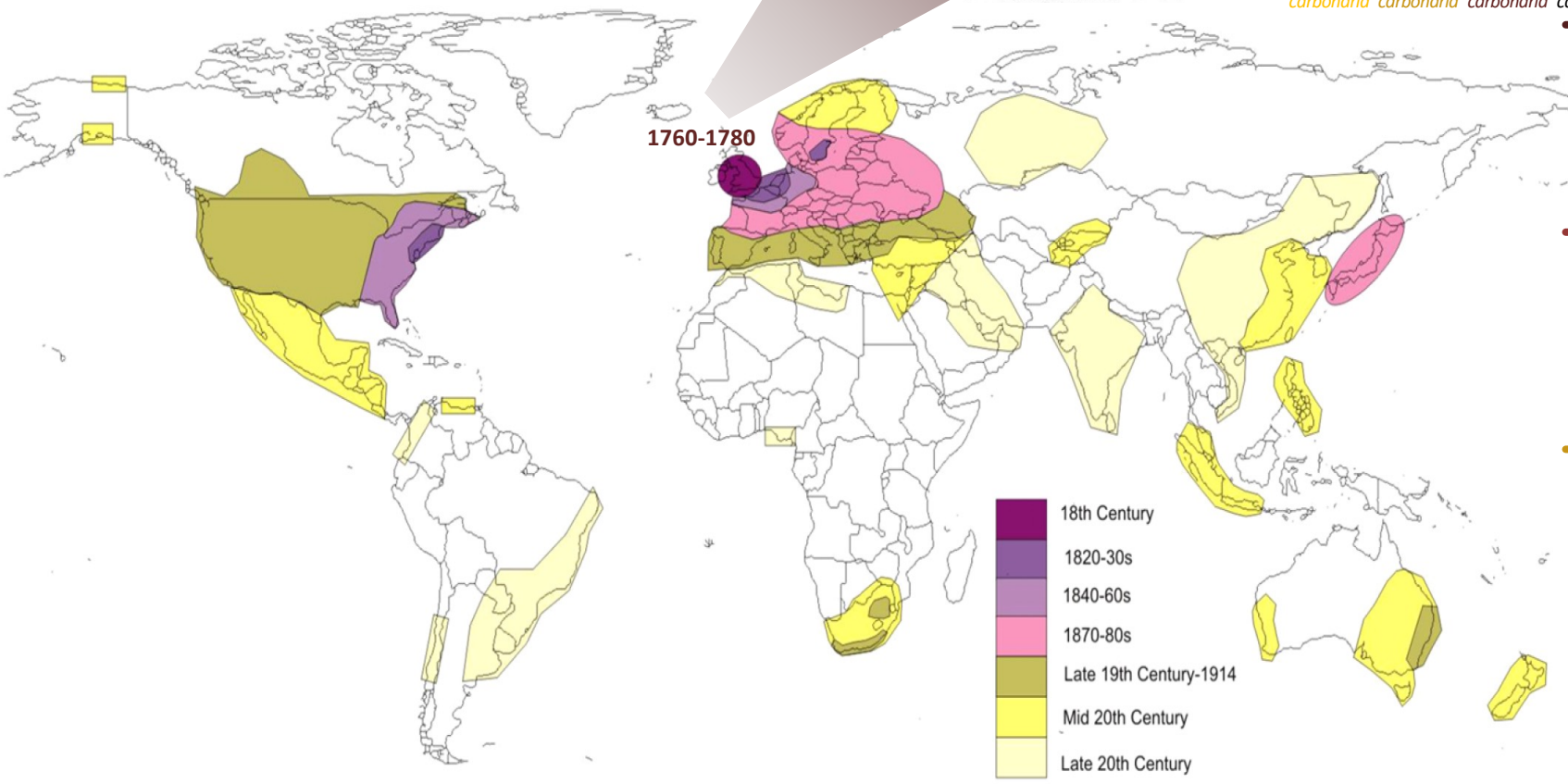
Urban-industrial epoch



Frequence distribution map of the melanic form of pepper moth Biston betularia (carbonaria) relative to the light colored form (as indicated with circles of light yellow to black color) and major industrial centers (red rectangles) in Great Britain in the 1950s (Source: http://abacus.bates.edu/acad/depts/biobook/EvMelanism.htm)

30-60% *carbonaria* | 30-60% *carbonaria* | 60-80% *carbonaria* | 80-100% *carbonaria* | Industrial Center



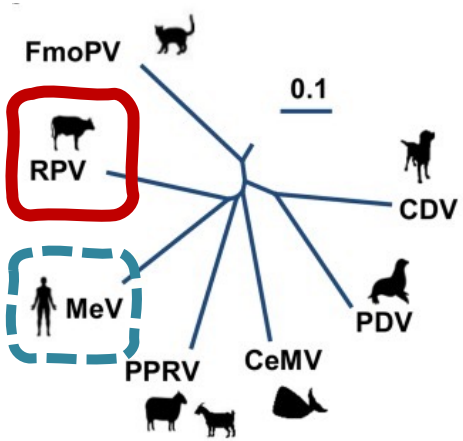


Sites and approximate dates of birth of Urban (Industrial) Revolution

Source of the figure:
A Stratigraphical Basis for the Anthropocene. Geological Society, London, Special Publications 395 (2014) Fig. 3

The changes brought about by humans on their lifestyle and their environment are affecting in various ways the evolution of other organisms and humans themselves. Examples of rapid changes in the environment and in nonhuman species are numerous and especially evident in recent years, after urban revolution, with impacts that often deflect back to humans in unpredictable ways.

A cattle virus pandemic caused by humans that had a profound impact on human history



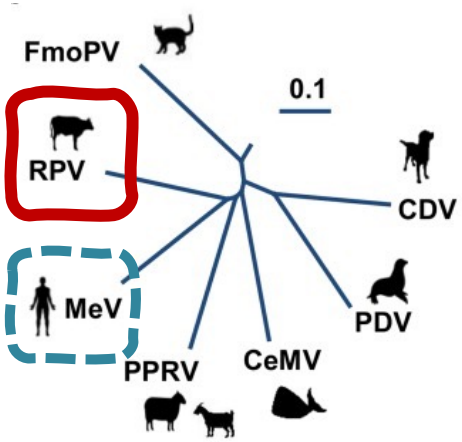
Morbillivirus
(ssRNA ιοί)

The **cattle plague virus** (rinderpest virus, RPV) is closely related to the measles virus (MeV) but RPV does not infect humans. RPV infects even-toed ungulates (artiodactyls), mainly cattle, buffaloes, giraffes, antelopes, deer, but also wildebeests (gnu) and warthogs (*Phacochoerus*).

The pandemic of cattle plague (rinderpest) in Africa towards the end of the 19th century had multiple direct and indirect impacts to human life (environment, crops, economy, health) that were becoming apparent during more than one century.

"I came from there to here without seeing an ox" (the "Great Ethiopian Famine" of 1887-1892)
Photograph from Transvaal, South Africa (ca. 1896)

A cattle virus pandemic caused by humans that had a profound impact on human history



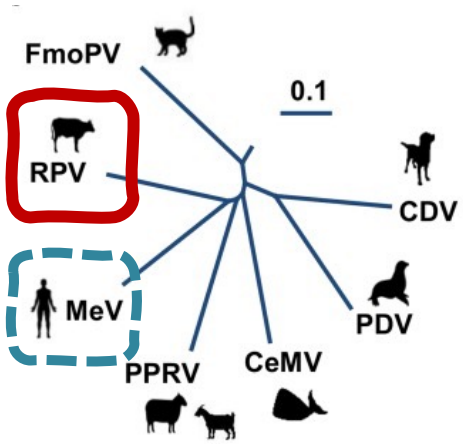
Morbillivirus
(ssRNA viruses)

Rinderpest virus (RPV) was endemic in the steppes of Asia and **had been historically introduced for several times in Europe** (where it had occasionally caused local epidemics), but it was introduced in Africa for the first time only at the end of 19th century (1884-1889, initially in Somalia and Sudan and after 1890 in sub-Saharan Africa). The animals from Eurasia had already shared a long **coevolution history** with RPV (for that reason, they were relatively resistant to the virus and the virus was modestly infective to them). **The animals in Africa, however, were immunologically naïve hosts of the virus**.

Key source:

Morens *et al*. (2011) *J. Infect. Dis.* 204, 502-505
Global rinderpest eradication: Lessons learned and why humans should celebrate too.

A cattle virus pandemic caused by humans that had a profound impact on human history



Morbillivirus
(ssRNA viruses)

What was the impact of the RPV introduction to Africa?

(1) Direct impact:

- Cattle plague (rinderpest) virus pandemic in Africa (initially in the decade 1890-1899)
- **Eradication of 90% of cattle** and buffaloes (as well as some species of antelope) in East and South Africa. Dramatic change of the distribution of all other species of even-toed ungulates affected.
- **Rural and nomadic populations of humans** lost their animals and suffered massively from **famine and endemic smallpox outbreaks**. Such phenomena were recurring for many years due to repetitive epidemics of rinderpest (1917-18, 1923, 1938-41).

Key source:

Morens *et al*. (2011) *J. Infect. Dis.* 204, 502-505
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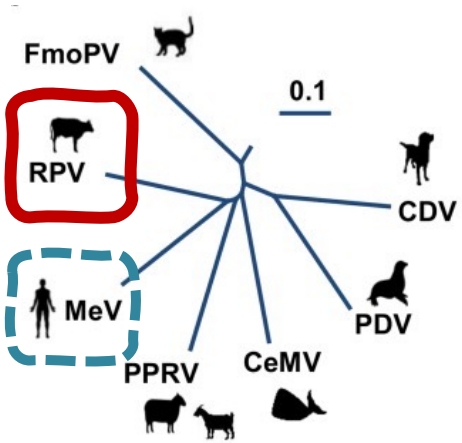

Morbillivirus
(ssRNA viruses)

What was the impact of the RPV introduction to Africa?

(2) Indirect impact:

- **Disappearance of insects** (tsetse flies) **that used to feed on vulnerable herbivore animals** at the relevant areas (previously being farming areas with trees and shrubs).
- **Change of the predation strategies of predators** (lions) **due to lack of prey** (including even the appearance of man-eating lions), urging farmers and herders to abandon large areas of cultivated lands, which gradually changed to non-cultivable areas with sporadic bunches of shrubs or trees.

Key source:

Morens *et al*. (2011) *J. Infect. Dis.* 204, 502-505
Global rinderpest eradication: Lessons learned and why humans should celebrate too.

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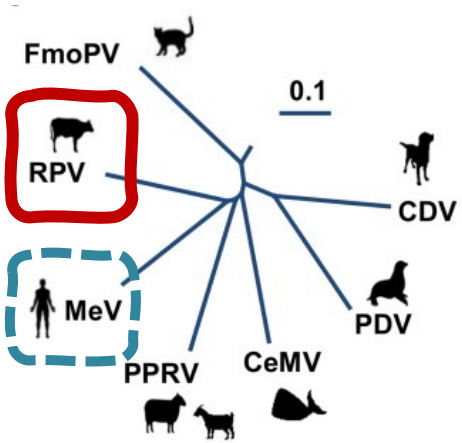


Morbillivirus
(ssRNA viruses)

What was the impact of the RPV introduction to Africa?

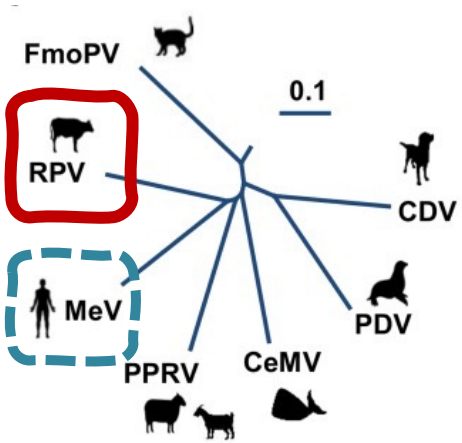
(3) Indirect impact, in later years:

- **Wild animals** that developed immunity to RPV **returned to the abandoned rural areas** along with **tsetse flies** which were using them as their hosts. Predators (lions) resumed using strategies of predating on even-toed ungulate preys.
- Due to the risk of being bitten by tsetse flies that were vectors of protozoan trypanosomes causing trypanosomiasis (sleeping sickness), **human populations completely abandoned** these areas, which are now designated as National Parks of countries of the East and Central Africa.

Key source:

Morens *et al*. (2011) *J. Infect. Dis.* 204, 502-505
Global rinderpest eradication: Lessons learned and why humans should celebrate too.

A cattle virus pandemic caused by humans that had a profound impact on human history



Morbillivirus
(ssRNA viruses)

What is the overall picture of these changes ?

- RPV **changed the ecological structure of almost 50% of a whole continent** for over a century.
- Consequences on humans were mostly indirect, but **dramatic and non predictable *a priori***.
- Consequences of the introduction of RPV in Africa were similar to the consequences of the introduction of measles (MeV) and smallpox viruses from the Columbus crew arrival in America to the New World inhabitants!
- **A major campaign for animal vaccination against rinderpest** (based on a vaccine that had already been developed in the period 1956-1962 by W. Plowright) eventually led, very **recently** (**2011**), to the **global eradication of rinderpest** (World Organization for Animal Health, https://www.oie.int/for-the-media/rinderpest/).

Key source:

Morens *et al*. (2011) *J. Infect. Dis.* 204, 502-505
Global rinderpest eradication: Lessons learned and why humans should celebrate too.

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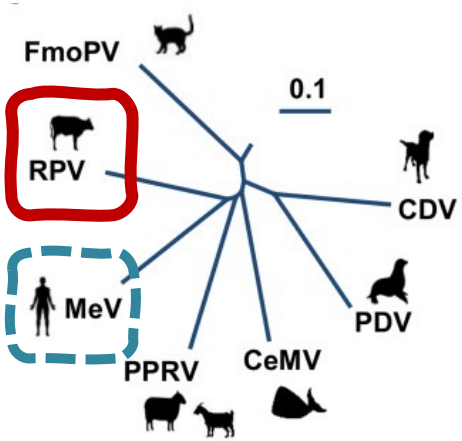


Morbillivirus
(ssRNA viruses)

How was this domino of changes initiated ?

The cattle in Africa were immunologically naïve to the rinderpest virus (RPV), because RPV virus was only transferred to Africa with the massive cattle transportation from Asia and Europe by nomadic herders in the last decades of 19th century.

"I came from there to here without seeing an ox" (the "Great Ethiopian Famine" of 1887-1892)
Photograph from Transvaal, South Africa (ca. 1896)

Key source:

Morens *et al*. (2011) *J. Infect. Dis.* 204, 502-505
Global rinderpest eradication: Lessons learned and why humans should celebrate too.

Evolution of the microbiome and of bacterial resistance to antibiotics after the discovery of antibiotics by human.

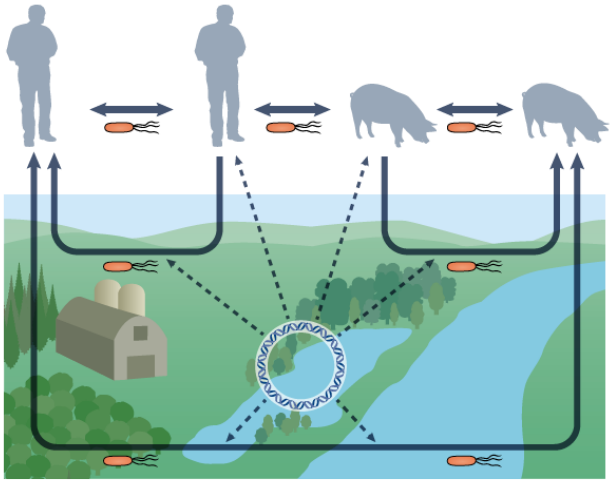
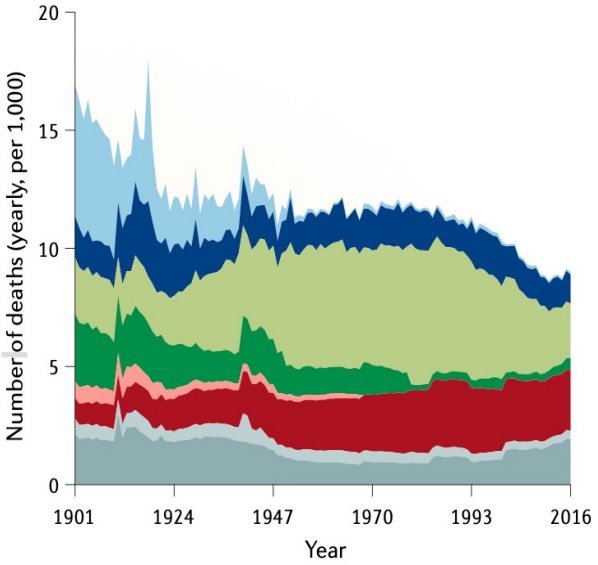


Figure source: Larsson, D. J., and Flach, C.-F. (2022). Antibiotic resistance in the environment. *Nat. Rev. Microbiol.* 20, 257-269. Figure 3.

The establishment of Public Health laws and practices, the development of vaccines and the discovery and use of antibiotics on a global scale led to a sharp decrease of the deaths from infections in the first half of 20th century!



In parallel, there was a gradual rise in deaths from noninfectious diseases, like cardiovascular (light green), neurological (green) and cancer (red) (Figure source: Corbett *et al.* (2018) *Nat Rev Genet* 19, 419-430. Figure 3).

Pandemic of Hispanic flu (1918)

Deaths due to infections per year per 100,000 (in USA)

800
600
400
200
0

Clinical use of sulfonamides

Clinical use of penicillin

The widespread use of antibiotics has been linked to a global rise of microbial resistance

First report of bacterial resistance to penicillin

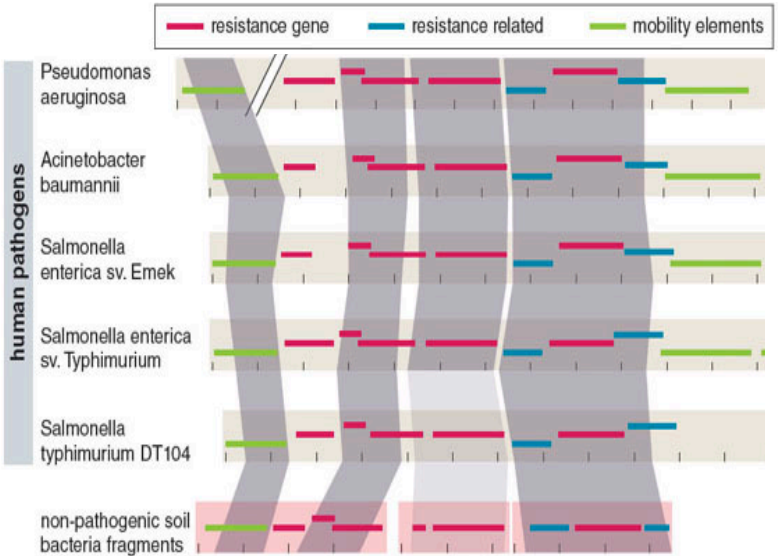
US Public Health Service

US Food and Drug Administration

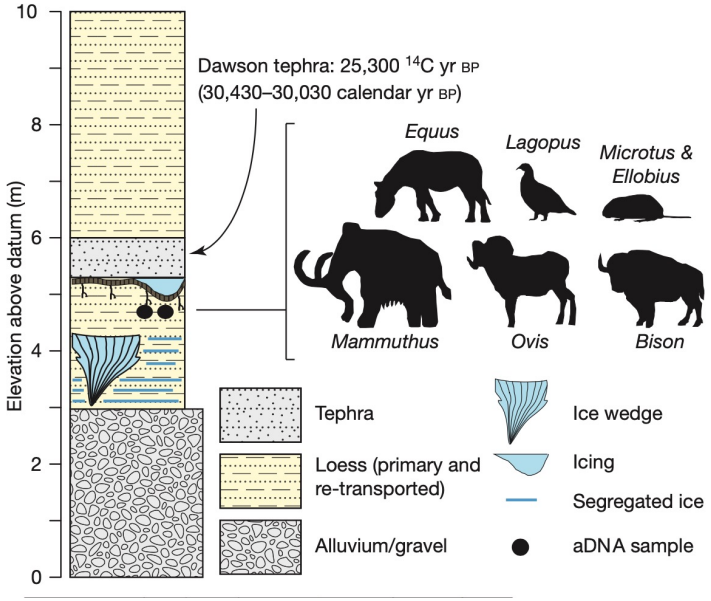
World Health Organization

1910 1920 1930 1940 1950 1960 1970 1980 1990

Resistance of bacteria to antibiotics («antimicrobial resistance») has been known in natural environments and mammalian microbiomes since ancient times.



Forsberg *et al.* (2012). The shared antibiotic resistome of soil bacteria and human pathogens. *Science* 337, 1107-1111.



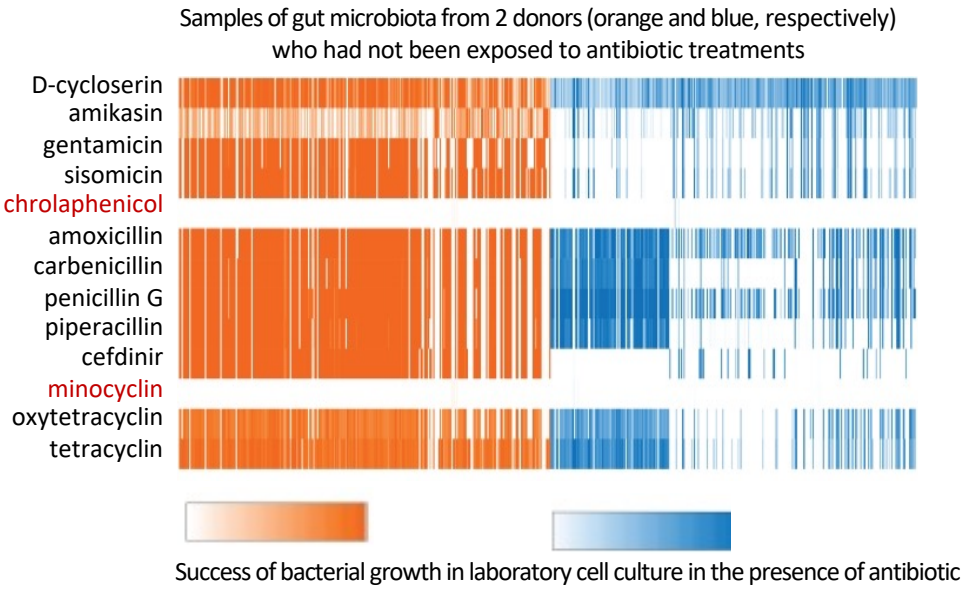
D' Costa *et al.* (2011). Antibiotic resistance is ancient. *Nature* 477, 457-461.

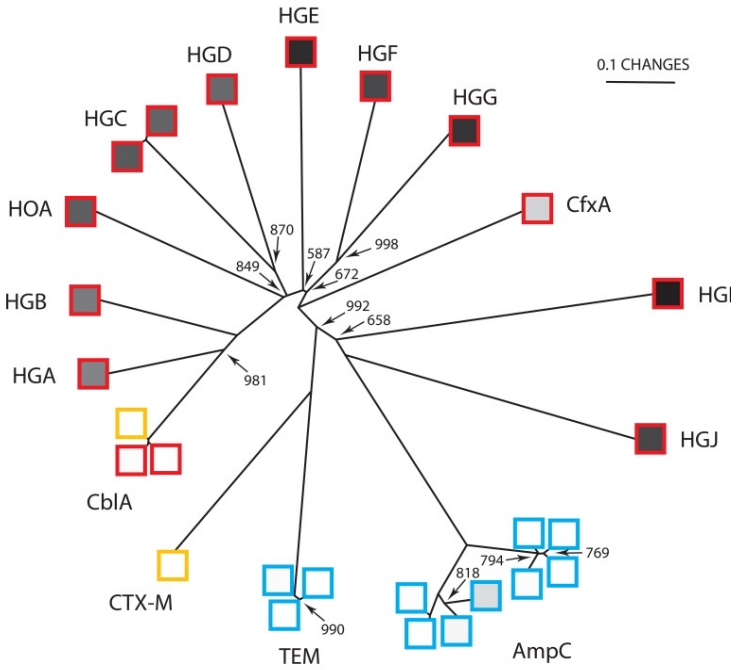
Several (non pathogenic) soil bacteria possess antibiotic resistance genes that are similar to genes in common pathogenic bacteria.

This finding, of course, makes sense:
Antibiotics and antibiotic resistance mechanisms are naturally produced by microorganisms that have been evolving on Earth for billions of years.

Samples of a permafrost sediment in Alaska (dated to 30 thousand years ago) contain DNA of animal microbiome with antibiotic resistance genes that are similar to genes of common present-day pathogenic bacteria.

The gut microbiome includes bacteria with various antibiotic resistance genes even before exposure of the human organism to treatment with antibiotics.





Gut microbiomes contain various resistance genes even before exposure of the organism to antibiotic treatments. In addition, the gut microbiomes contain a multitude of bacteria that are sensitive to each one of the antibiotics tested (no growth; white color sites in the figure).

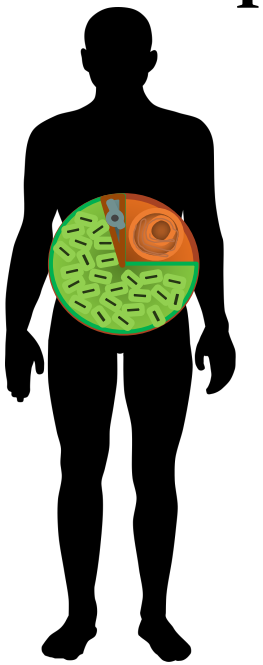
Antibiotic resistance genes of the human gut microbiomes vary and, in general, differ significantly in sequence from antibiotic resistance genes isolated from pathogen cultures or aerobic cultures in the lab.

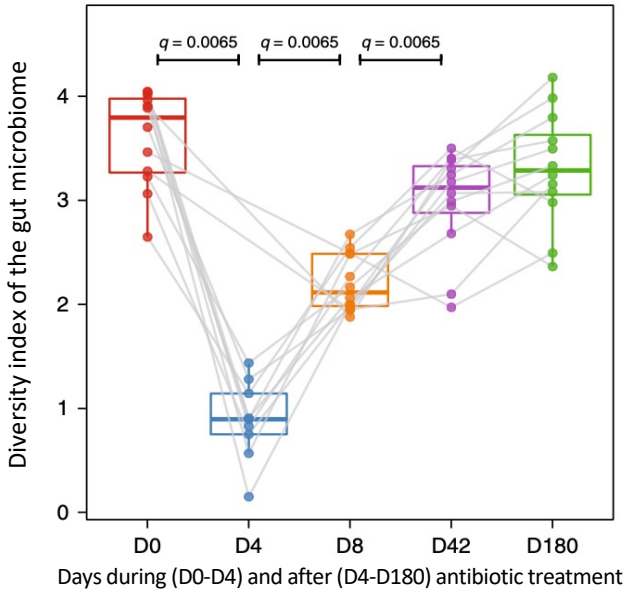
Derived from gut microbiome

Derived from aerobic cultures

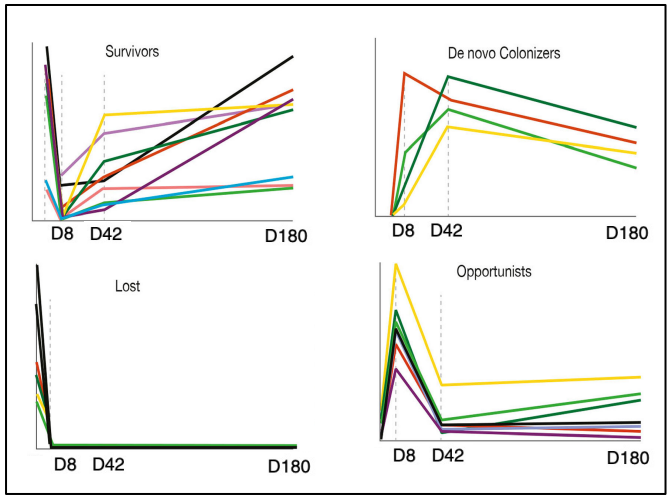
Sommer *et al.* (2009). Functional characterization of the antibiotic resistance reservoir in the human microflora. *Science* 325, 1128-1131.

Frequent exposure of human organism to antibiotics (reinforced by excessive or inadvertent usage and through the dispersal of resistant bacteria in the environment) **alters the population structure of gut microbiome.**

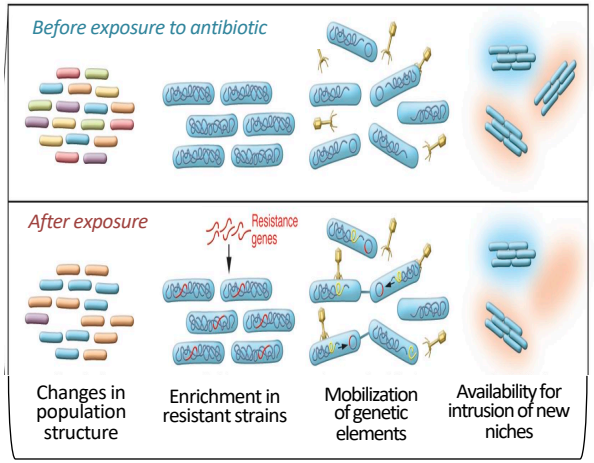




Palleja *et al.* (2018). *Nat. Microbiol.* 3, 1255–1265.



Ramirez *et al.* (2020). *Front. Cell. Infect. Microbiol.* 10: 572912.

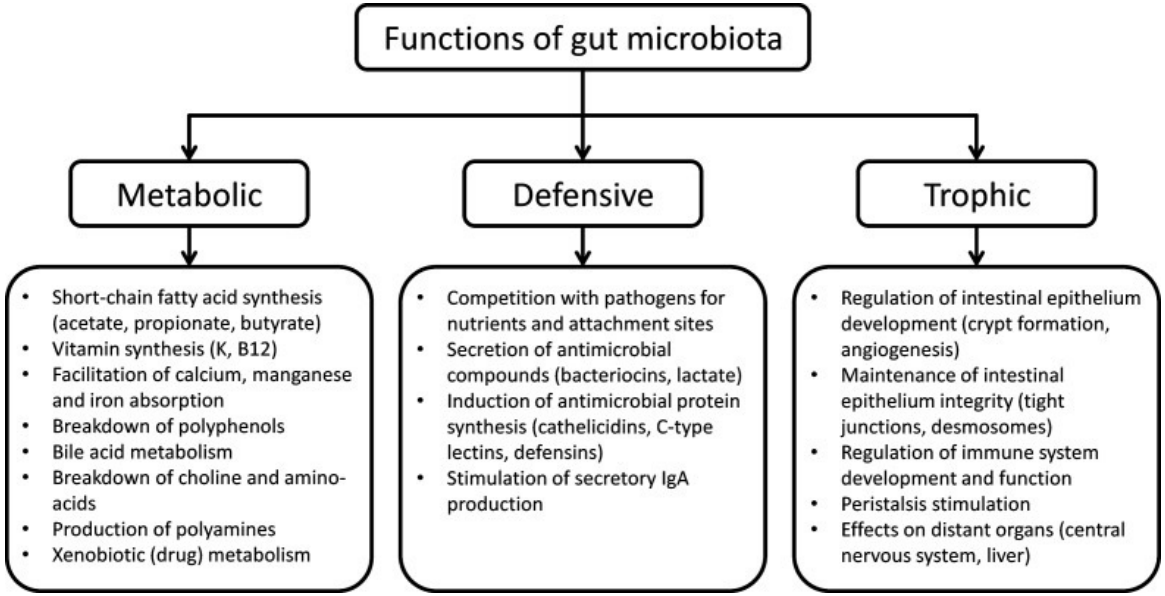


Modi *et al.* (2014) *J. Clin. Invest.* 124, 4212-4218.

A four-day antibiotic treatment decreases dramatically the diversity index of the microbiome (above, D0-D4). Diversity recovers slowly in the following 6 months (D4-D180) but the composition of bacterial species and strains changes. Some bacterial species may disappear (Lost, upper right). Apart from enrichment in antibiotic-resistant strains (due to selection), exposure to the antibiotic changes genetic, metabolic and ecological features of the microbiome (bottom right).

Losses of microbiome diversity due to the extensive use of antibiotics but also due to decreased exposure to new microbial species in modern urban environments **lead to dysfunctions.**

Figure source: Scudellari (2017). *Proc. Natl. Acad. Sci. USA* 114, 1433–1436. Figure 1

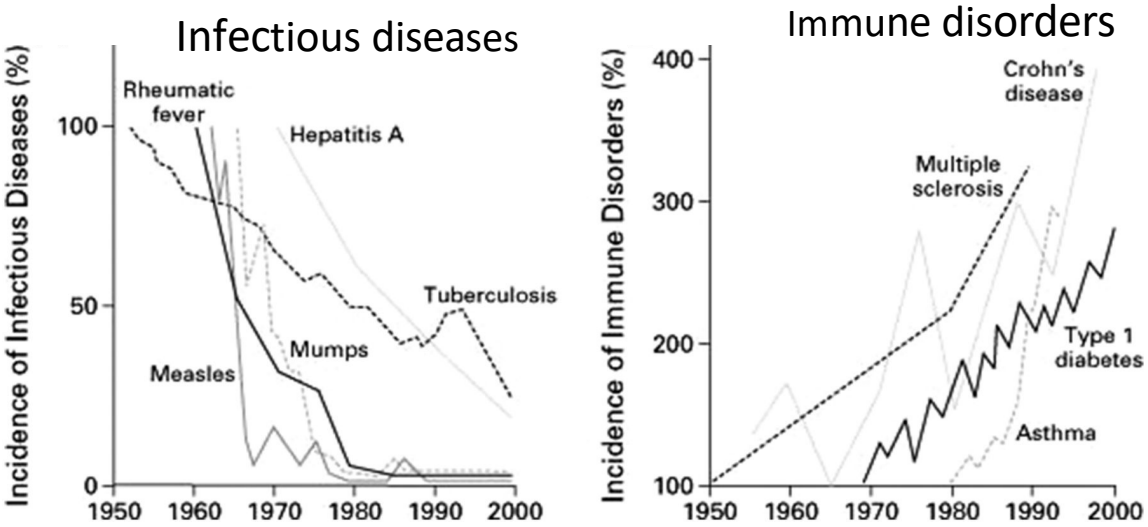


Ramirez *et al.* (2020). *Front. Cell. Infect. Microbiol.* 10: 572912. Figure 1
(based on: Guarner & Malagelada (2003). *Lancet* 361, 512-519.)

The human gut microbiome has many roles, in metabolism (e.g., synthesis of vitamins and short-chain fatty acids, facilitation of iron and calcium absorption, breakdown of complex polysaccharides, metabolism and processing of toxins and excess drugs), in defense (control of the growth of pathogens) and in regulation of the development and function of the intestinal epithelium and the immune system. Microbiome biodiversity is important in all these functions.

Losses of microbiome diversity due to the extensive use of antibiotics but also due to decreased exposure to new microbial species in modern urban environments **lead to dysfunctions.**

Figure source: Scudellari (2017). *Proc. Natl. Acad. Sci. USA* 114, 1433–1436. Figure 1

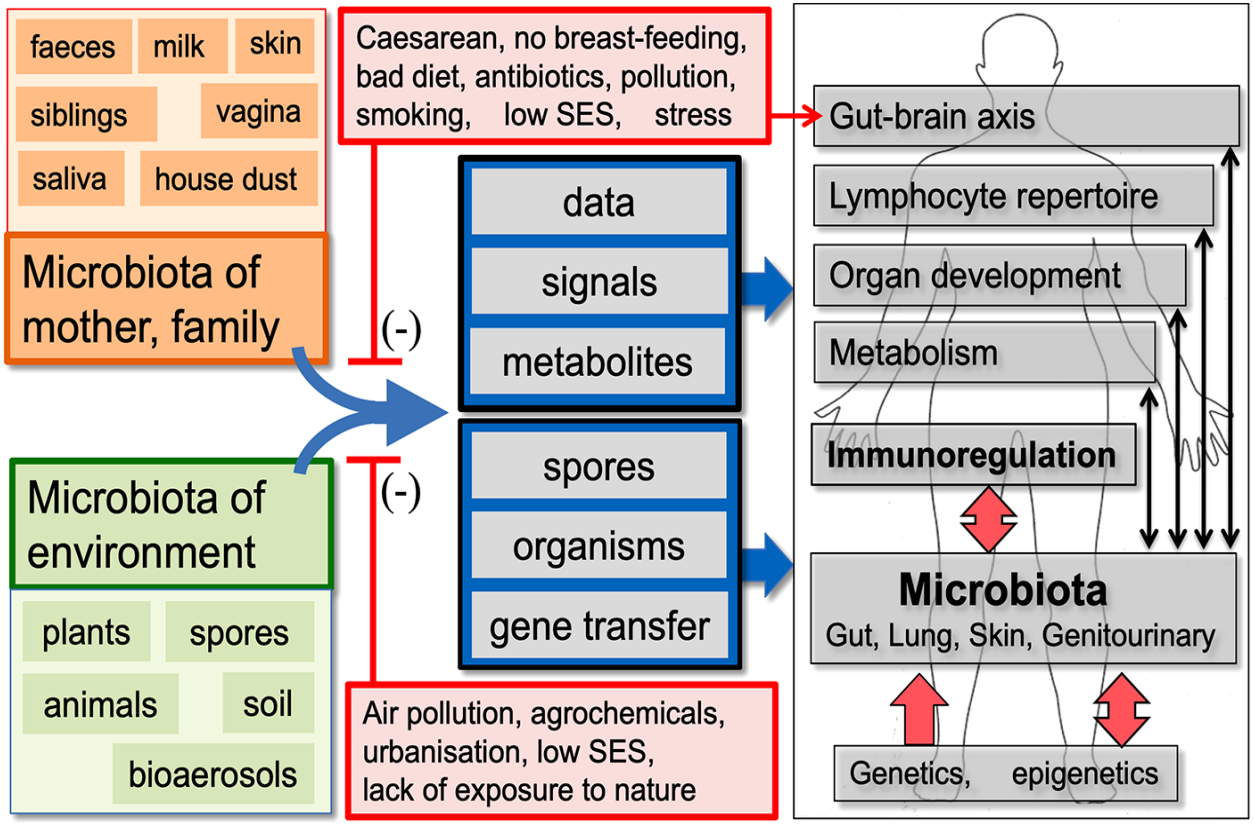


Inverse epidemiological relationship between infectious diseases (decrease of incidence) and immune disorders (increase of incidence).

Figure source: Scudellari (2017). *Proc. Natl. Acad. Sci. USA* 114, 1433–1436. Figure 2 (based on Bach (2002) N. Engl. J. Med. 347, 911-920.)

The decrease in microbiome biodiversity resulting from decreased exposure to bacteria from the environment (and from the microbiome of the mother at infant age), and increased exposure to factors (like antibiotics) disrupting the microbiome diversity, has consequences that have been correlated with problems in immune regulation and with the increase of the incidence of immune disorders (allergies, chronic inflammation, autoimmune disorders).

The inverse relationship between the **decrease** in **frequency** of **infectious diseases** and the **increase** in **frequency** of **immune disorders** has been interpreted with the **Hygiene/Old Friends hypothesis** (Rook, 2003).

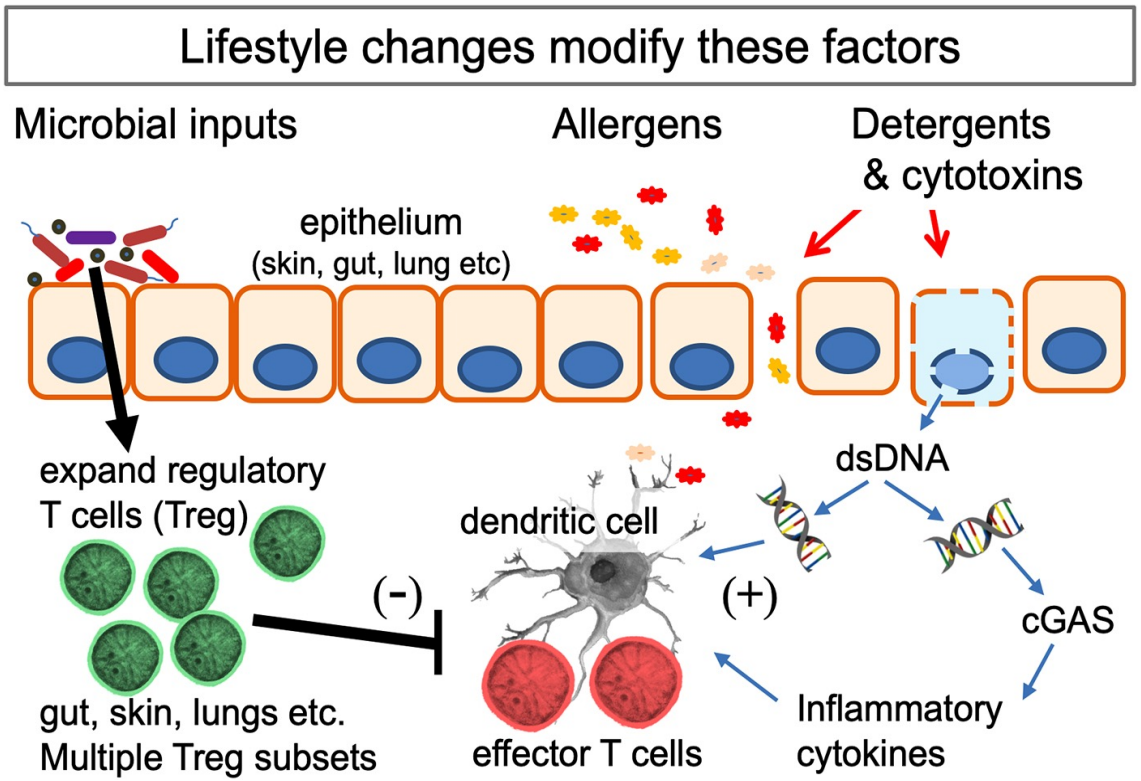


Source: Rook, *Front. Allergy* (2023); Figure 1

SES = socioeconomic status

The biodiversity of the human microbiome is limited in modern societies, but most important for **function of our immune system** is the **loss of microbiota species** with which we have coevolved for thousands of years. These microbiota are indispensable for the **development of the regulatory elements of the immune system.**

The inverse relationship between the **decrease** in **frequency** of **infectious diseases** and the **increase** in **frequency** of **immune disorders** has been interpreted with the **Hygiene/Old Friends hypothesis** (Rook, 2003).



Source: Rook, *Front. Allergy* (2023); Figure 2

Treg = regulatory T cells

Microorganisms that are needed for development of the regulatory elements of immunity (like regulatory T cells) are derived from the microbiome of the mother and close relatives as well as from the environment (including animals, soil, plants, spores) (see the figure in the previous slide). The modern lifestyle reduces exposure to these sources and exposes to factors that disrupt the crucial regulatory part of our microbiome.

The rise of evolutionary mismatch diseases in modern environments

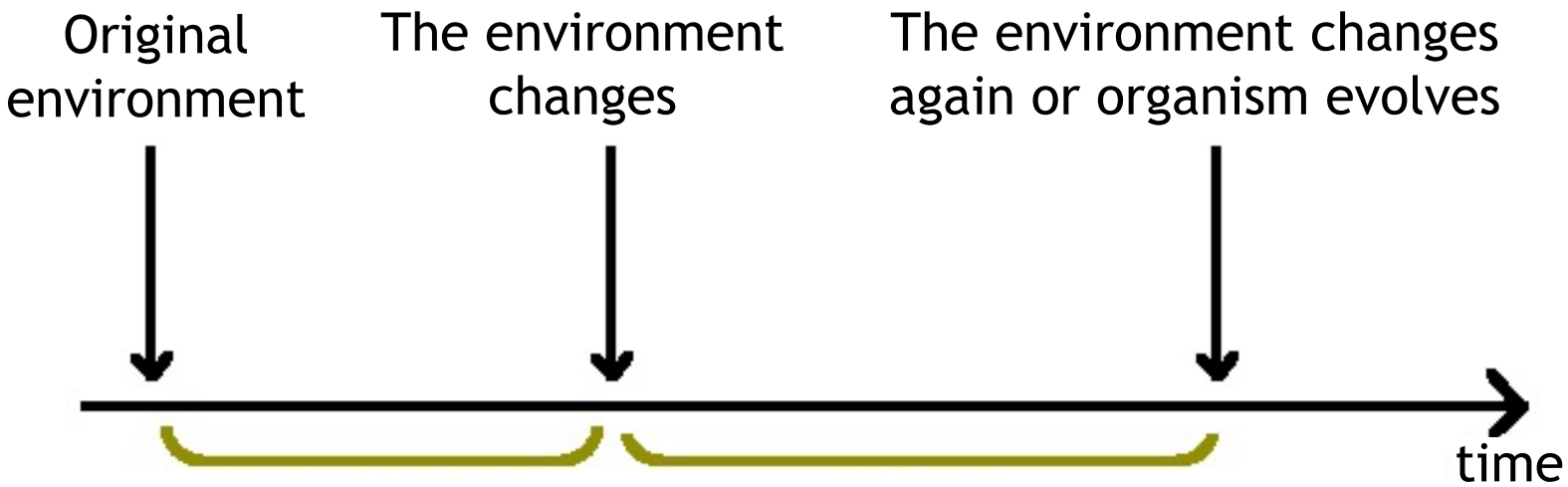
Source: Michigan State University Evo-Ed site; Lactase persistence. https://evo-ed.org/lactase-persistence/biological-processes/

Source: Lea *et al.* (2023). *PLoS Biol.* 21: e300231. Figure 2A (i)

Source: Lea *et al.* (2023). *PLoS Biol.* 21: e300231. Figure 2A (ii)

What is evolutionary mismatch?

A recent or rapid change in the environment «entraps» a previously neutral or beneficial trait in a maladaptive role.



Characteristic (trait) neutral or beneficial

The same characteristic assumes a harmful role in the new environment (is mismatched to the new environment; but remains common in the population because it had evolved at different conditions: "evolutionary trap")

The evolutionary relevance of a characteristic (and mutations linked to this characteristic) can change when the environment changes.

The same set of mutations (a genotype) responds differently in different conditions of natural selection.

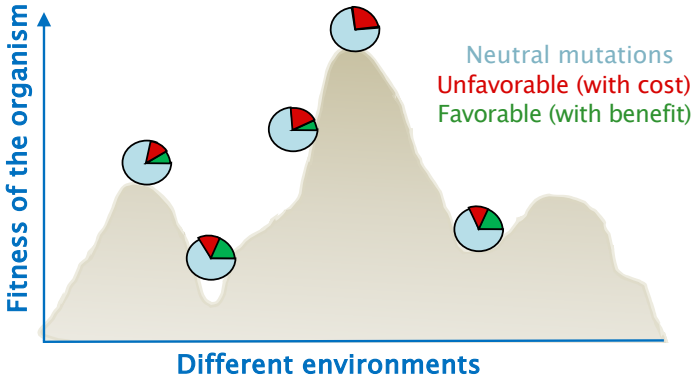


Figure design based on a drawing idea from: Duffy, *PLoS Biol.* 16: e3000003 (2018); Fig. 2

The burden of unfavorable mutations in each genotype changes depending on the environment.

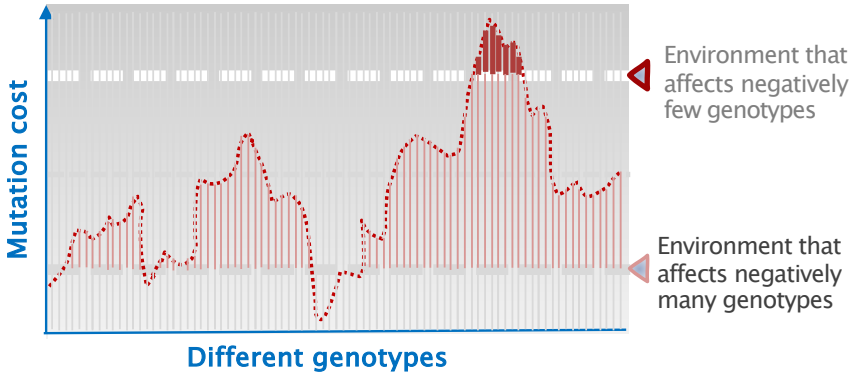


Figure design based on a drawing idea from: Stearns, S. C., *Principles of Evolution, Ecology and Behavior*, Lecture: Evolutionary Medicine. Open Yale Courses. https://oyc.yale.edu/ecology-and-evolutionary-biology/eeb-122/lecture-21

Human activity has shaped new (anthropogenic) environments that differ markedly from natural environments.

Recent anthropogenic (man-made) changes in the environment

Neolithic (Agricultural) Revolution

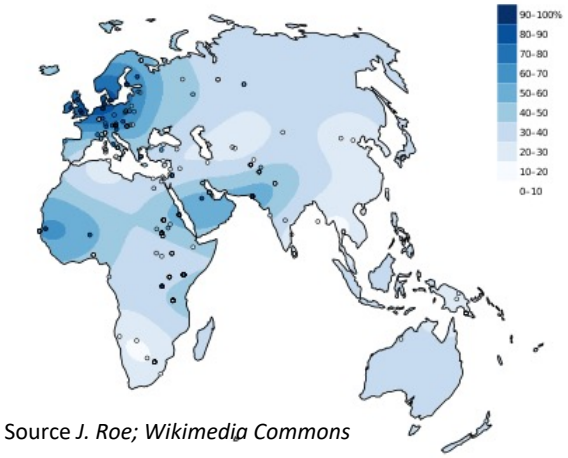
Transition from a nomadic hunter-gatherer lifestyle to the establishment and exploitation of permanent agricultural settings. *7-12 million years ago (initially in Mesopotamia, and then, independently, in other regions)*

Urban (Industrial) Revolution

Mechanization of agriculture and textile manufacturing; revolution in use of power; demographic, epidemiological and ecological transitions; pollution in big cities, change of use of cultivated lands and natural soils, climate change, overconsumption of sources, impacts on biodiversity. *200-250 years ago (until today)*

The recent anthropogenic changes lead to evolutionary mismatches.

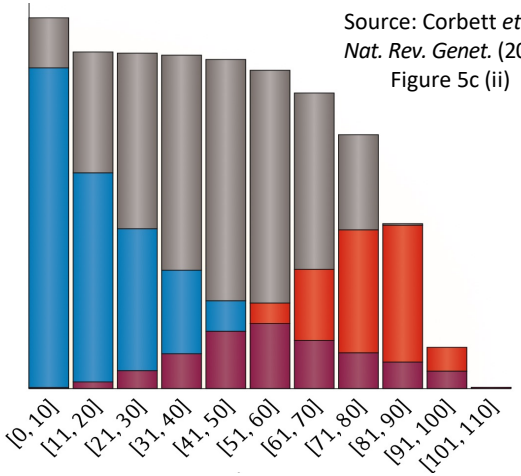
Evolutionary mismatches due to lifestyle changes traced to few thousands of years ago (neolithic revolution) have partially been reversed during evolution, through natural selection. Example: lactose intolerance and tolerance.



Source *J. Roe; Wikimedia Commons*

Intolerance and **tolerance** to lactose

Evolutionary mismatches due to changes traced to recent years (urban revolution) relate to more recent changes that reflect **a modern evolutionary transition**.
Example: Mismatch diseases like diabetes and obesity, cardiovascular diseases, or diseases related to ageing (figure on the bottom right).



Source: Corbett *et al.*, *Nat. Rev. Genet.* (2018) Figure 5c (ii)

Benefits and costs of characteristics per age group (superposed on recent demographic data (France, 2016))

The recent anthropogenic changes lead to evolutionary mismatches.

Evolutionary mismatches due to changes in recent anthropogenic environments have also been recognized and studied in nonhuman species (a key example is the ineffective orientation of sea turtle hatchlings towards the open horizon of the sea in shores polluted with lights from human activities), but the mismatch effects in human themselves are more prominent.

Source: U.S. Fish and Wildlife Service; *Wikimedia Commons*

Evolutionary mismatches are linked to major demographic, ecological and epidemiological transitions.

Urban revolution has promoted major **demographic** (changes in age structure of populations due to changes in birth and death rates, migrations and socioeconomic inequalities), **ecological** (urban environments, changes in conditions of living, working, sanitation, exposure to infections, accessibility to nutrition sources, change of land usage, biodiversity, climate change) and **epidemiological transitions** (major decrease in deaths from infections and increase of non-communicable (chronic) diseases).

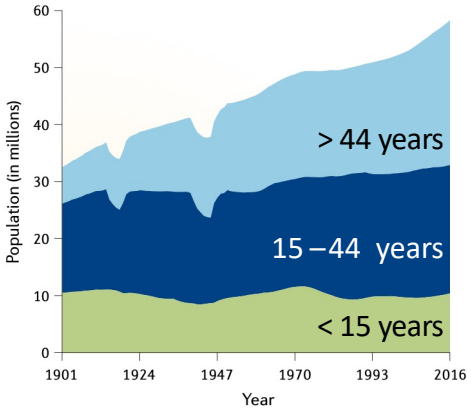
Evolutionary mismatches are linked to major demographic, ecological and epidemiological transitions.

Ecological transition

Urban
↑processed foods
↓physical activity
↓pathogen exposure
↑toxin exposure
⇅socioeconomic inequality
⇅social support

Transition from subsistence-level conditions to urban life conditions

Demographic transition



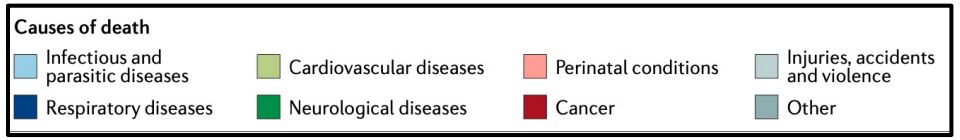
Increase of the middle- and senior-aged population

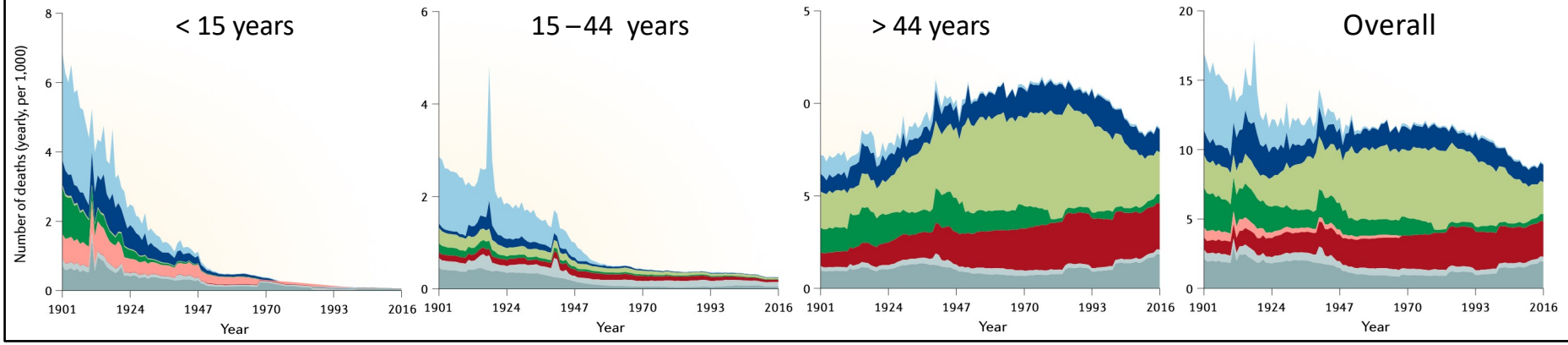
Data of demographic and epidemiologic transitions (England & Wales) from UK Office for National Statistics.

Source: Corbett *et al.* (2018) *Nat. Rev. Genet.* 19, 419-430. Figures 3 and 4.

Epidemiological transition

Decrease of deaths from infections and increase of deaths from chronic (non-communicable) diseases





What are the criteria for recognizing evolutionary mismatch diseases ?

1. They appear at higher frequencies in the new (modern) relative to the old (ancient) environment.

\+ 2. They are linked to an environmental parameter that differs in the new (modern) relative to the old (ancient) environment.

\+ 3. They are linked to genetic variants that had been fixed in the past through natural selection because they offered some advantage, or were evolutionarily neutral but had been co-selected in the same genetic locus with another, advantageous variant. In the new (modern) environment, the same variants are linked to the phenotype of the mismatch disease.

What are the criteria for recognizing evolutionary mismatch diseases ?

What is the available evidence?

1. Many non-communicable (chronic) diseases appear at higher frequencies in current times (like cardiovascular diseases, cancer, immunoregulation disorders, neurodegenerative diseases).

2. Many chronic diseases have been associated to environmental parameters that are common in the modern (urban) environment (cardiovascular diseases with lack of physical activity, immune disorders with loss of microbiota, neurodegenerative diseases with increase of lifespan etc.).

3. Establishing a link between a non-communicable disease and specific genetic variants is often difficult because chronic diseases are complex multifactorial diseases. The relevant genetic variants influence signal transduction pathways that usually have multiple effects on multiple phenotypes.

What are the criteria for recognizing evolutionary mismatch diseases ?

How could we assess evolutionary mismatch experimentally?

1. Evidence for the incidence or mortality of diseases comes from epidemiological data, which collectively cover a limited part of the history of modern epidemiological transitions.

2. Evidence for the differences in environmental parameters comes from historic, demographic and epidemiological records, which are also partial or absent for many geographical areas.

Recently, researchers have initiated studies of potential evolutionary mismatch transitions using the few human communities who persist in a subsistence-level lifestyle but are gradually becoming incorporated in urban-industrial environments.

3. Genetic polymorphisms have been linked to particular disease phenotypes based on polycentric genome-wide association studies and the relevant genetic loci have been studied experimentally in model organisms (such as in the nematode *C. elegans*, *Drosophila* fruit fly or mice), but without direct experimental reference to an evolutionary mismatch condition.

Can we really study the relationship of genes and environment in evolutionary mismatch diseases?

Subsistence-level
↓processed foods
↑physical activity
↑pathogen exposure
↓toxin exposure
⇅socioeconomic inequality
⇅social support

Urban
↑processed foods
↓physical activity
↓pathogen exposure
↑toxin exposure
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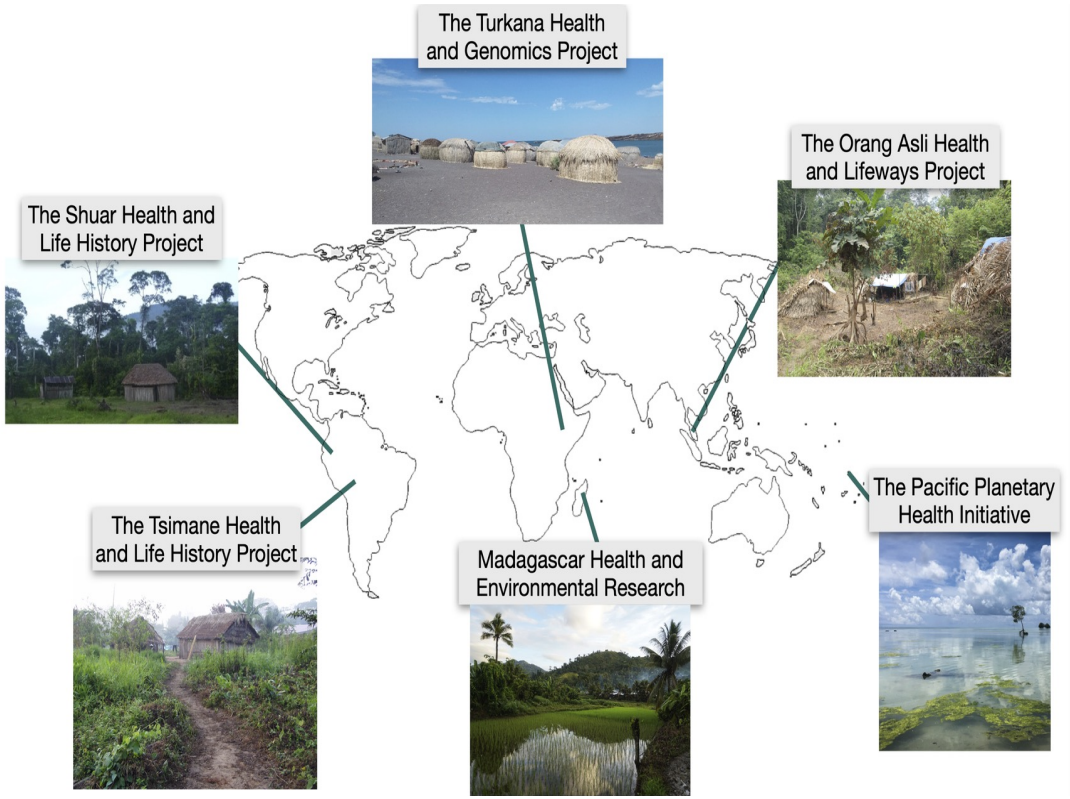
⇅social support

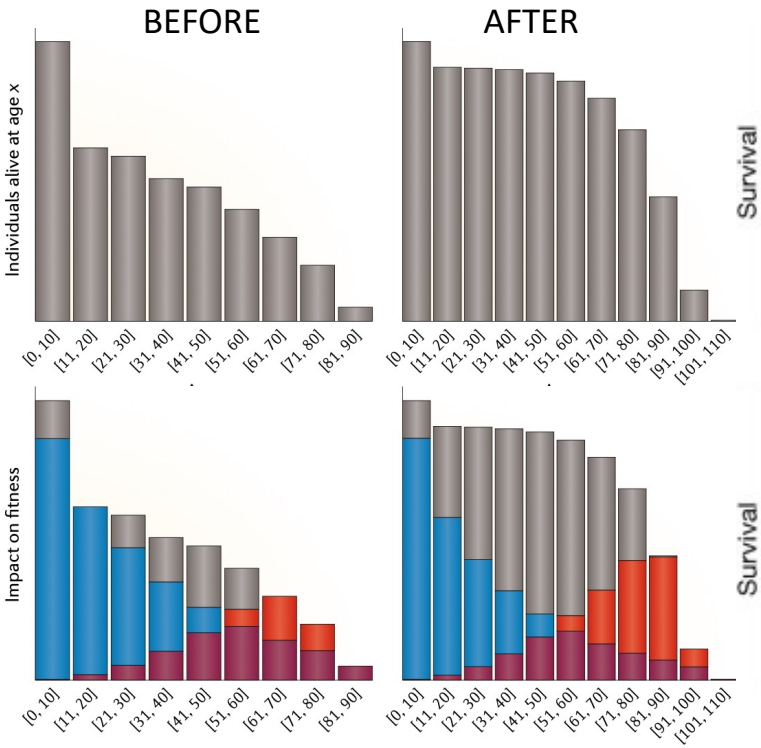


Source: Lea *et al.* (2023). *PLoS Biol.* 21: e300231. Fig. 2

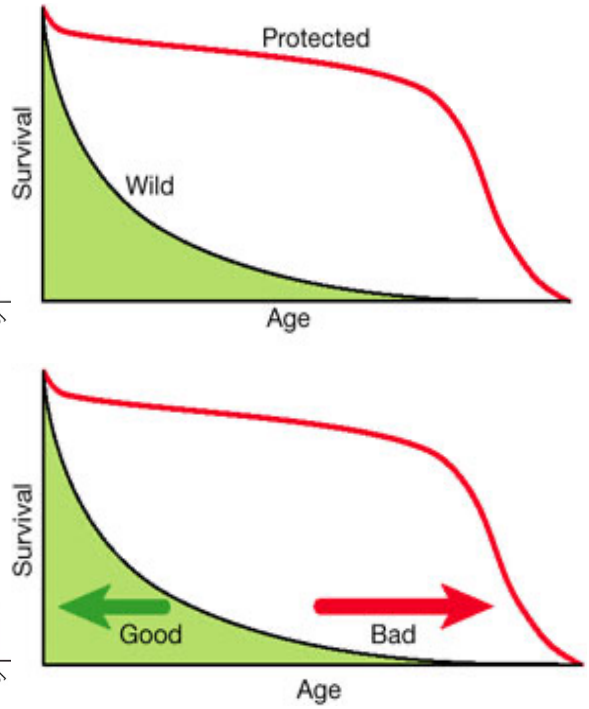
An ongoing recent study that attempts to emulate the comparison of modern-time with pre-industrial conditions has been initiated with population communities in the world that are considered as a model of humans who persist in a subsistence-level lifestyle but are currently exposed to globalizing forces for incorporation to modern urban environments (i.e., simulation of the **transition to a state of evolutionary mismatch**). These studies compare ecological, cultural, anthropological and biomedical data with analyses of the genomes.

An important concept for understanding the relationship of genes and environment in mismatch diseases: Antagonistic pleiotropy

Age structure of human populations before and after the evolutionary transition to the modern (urban) conditions and the effect of characteristics that have benefit early in life and cost in older ages



Model of the age distribution of mortality in natural and in protected environments and the effect of pleiotropy



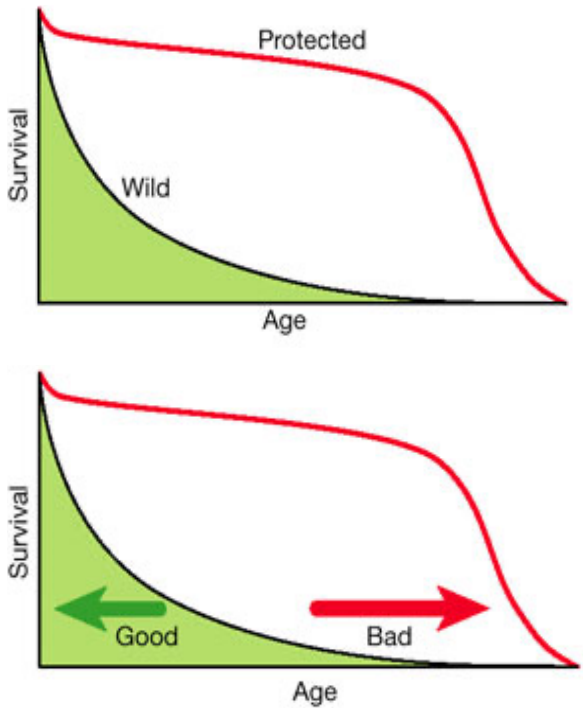
Genes that have been linked to evolutionary mismatch diseases manifesting in late ages usually have pleiotropic effects (they provide benefit that increases reproductive success early in life but have health cost in old ages). This property is called **antagonistic pleiotropy.**

Source: Corbett *et al.* (2018) *Nat. Rev. Genet.* 19, 419-430. Fig. 5 Kirkwood & Austad (2000) *Nature* 408, 233-238. Fig. 1

An important concept for understanding the relationship of genes and environment in mismatch diseases: Antagonistic pleiotropy

The concept of antagonistic pleiotropy was introduced by Peter Medawar (1952), but was elaborated further as an evolutionary condition that favors the modern epidemiological rise of **diseases related to ageing** by George Williams (1957). According to the theory of antagonistic pleiotropy, ageing is caused by a combined effect of many genes that had been favored in previous environments (when life expectancy was low) by **natural selection**, because they offer an advantage **at reproductive age**, even though they exert negative effects on survival in old ages.

Model of the age distribution of mortality in natural and in protected environments and the effect of pleiotropy



Kirkwood & Austad (2000) *Nature* 408, 233-238. Fig. 1

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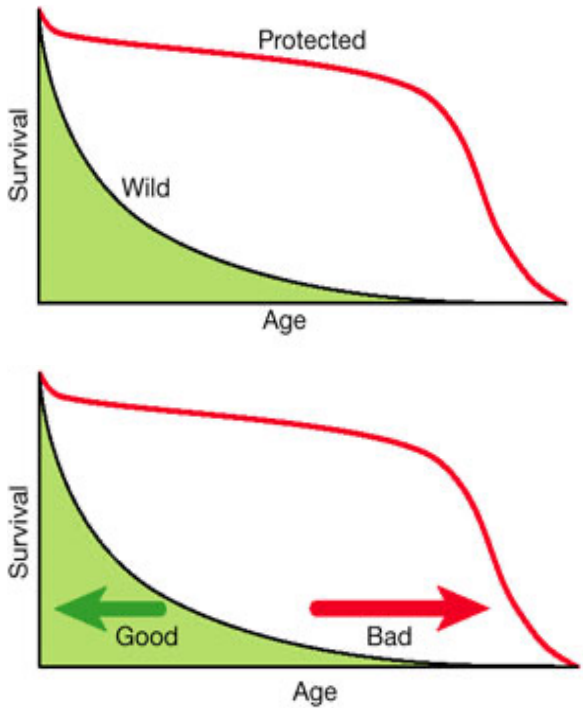
Model of the age distribution of mortality in natural and in protected environments and the effect of pleiotropy

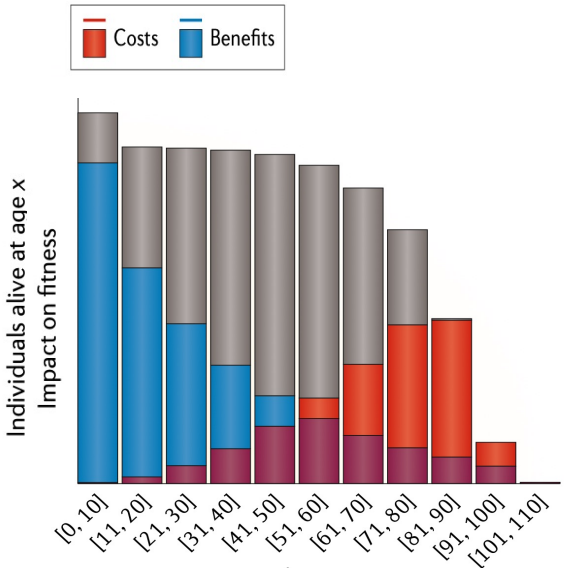


Kirkwood & Austad (2000) *Nature* 408, 233-238. Fig. 1

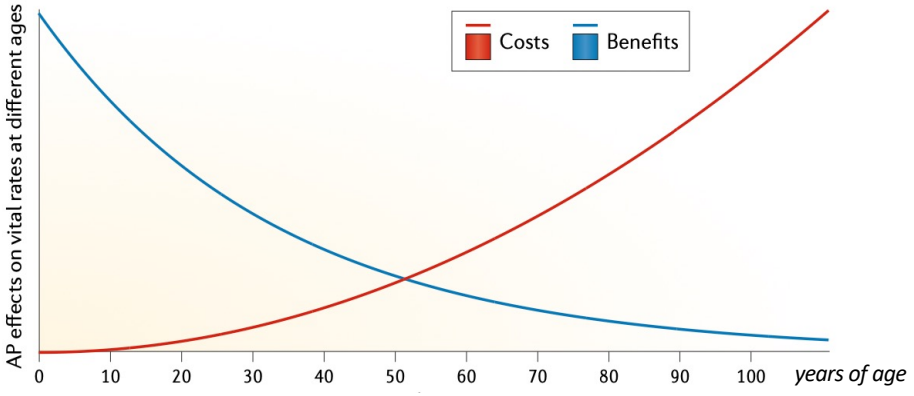
In fact, genes related to **antagonistic pleiotropy** usually have pleiotropic effects on multiple evolutionary mismatch diseases, such as genes of the **insulin/IGF-1** pathway (which is also controlled by growth hormone/GH) that has been linked with both insulin resistance, longevity and ageing.

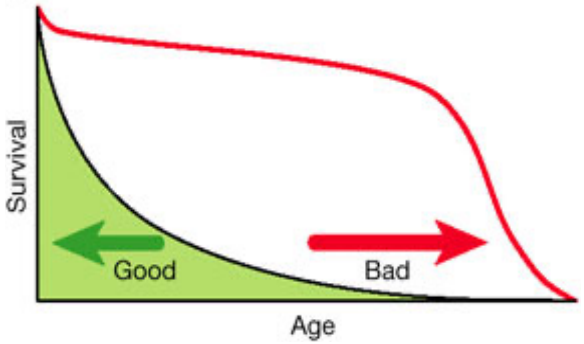
Conclusion
What is the field of Evolutionary Medicine

The antagonistic pleiotropy hypothesis was the first trigger that eventually led to development of the field of Evolutionary Medicine.



Source: Corbett *et al.* (2018) *Nat. Rev. Genet.* 19, 419-430. Fig. 5





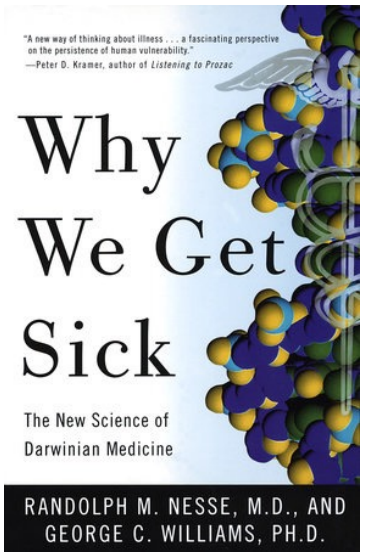
Source: Kirkwood & Austad (2000) *Nature* 408, 233-238. Fig. 1

George C. Williams
(evolutionary biologist)

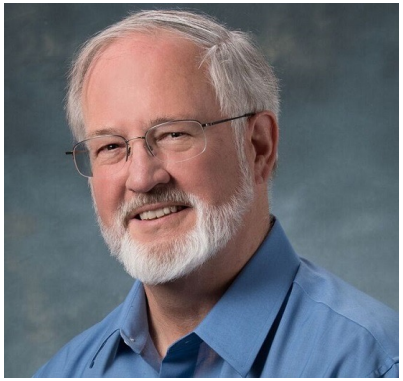
..1957

What is Evolutionary Medicine ..*1991*

A relatively new scientific discipline. It was founded by R. Nesse and G. Williams who introduced the term «Darwinian medicine» and discussed the relationship of human evolutionary history with modern diseases (neuropsychiatric, metabolic, immunological diseases) and ageing.



Why we get sick: the new science of Darwinian medicine. Vintage Books (1994)



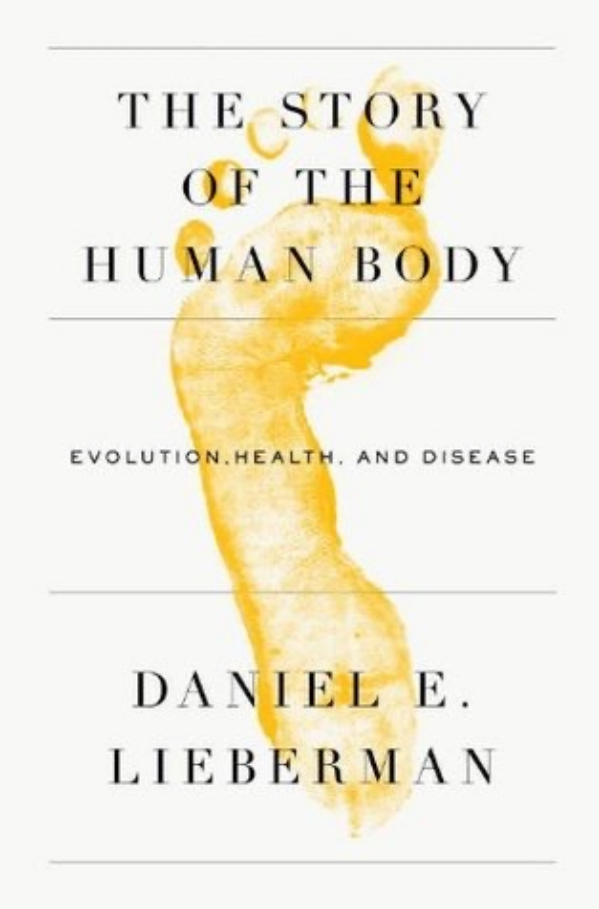
Randolph M. Nesse
(psychiatrist)

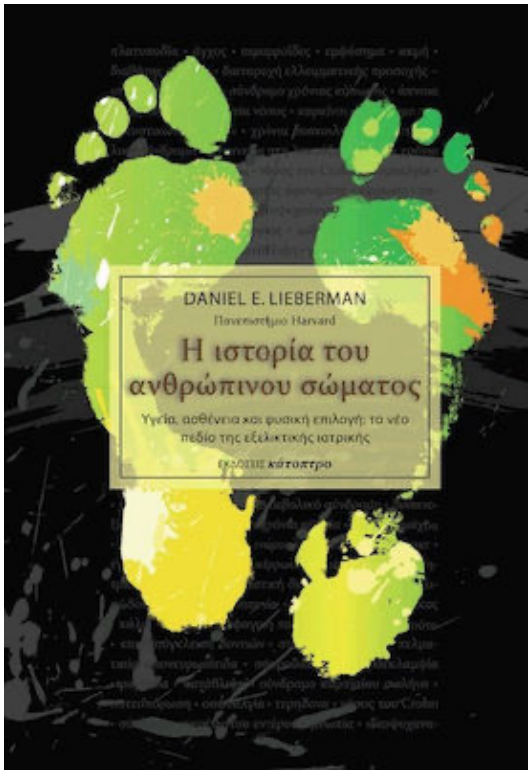
George C. Williams
(evolutionary biologist)

..*1957*

The dawn of Darwinian medicine (*Q. Rev. Biol.* 66, 1-22 (1991))

What is Evolutionary Medicine *..2013*





1. Apes and humans
2. Agriculture and Industrial revolution
3. Modern environments and diseases (present and future)

Daniel E. Lieberman, The story of the human body – evolution, health, and disease (translated and edited by: S. Sfendourakis, A. Karamanlidis, P. Delivorias), Greek edition, Katoptro Publications, Athens, 2015 (Lieberman, D. E., The story of the human body – Evolution, Health and Disease, *Pantheon Books*, 2013)

What is Evolutionary Medicine

A set of **concepts** and **approaches** derived from the Theory of evolution with which to analyze many different aspects of medical science. **Evolutionary** insights can enhance our ability to **understand**, **diagnose** and **heal** human diseases. [S.C. Stearns (2012) *Proc. R. Soc. B* 279, 4305-4321]

The evolutionary approach broadens our understanding of disease and the patient and illuminates their connection to the human evolutionary history.

- Similarities and variations in our genes and characteristics (traits) are being shaped through evolution. Our genetic diversity includes genes of different evolutionary ages, over the breadth of time of evolution of life on Earth. The part of diversity that is connected to health, well-being and diseases refers both to changes that have occurred thousands of years ago and to more recent changes.
- Diseases are apprehended as phenotypes that are defined by variations in genotype-by-environment interaction that have emerged during evolution. All individuals, either patient or healthy, are being shaped as bundles of cost-benefit tradeoffs with respect to their reproductive success in various environments to which they have been exposed during evolution.
- In recent evolutionary history, environmental changes that are attributed to the consequences of human cultural evolution (neolithic revolution and urban revolution) have led to evolutionary mismatch states and diseases.

Source commentary: *Proc. R. Soc. Darwin Review Series*
Stearns, S. C. (2012) Evolutionary medicine: its scope, interest and potential. *Proc. R Soc. B* 279, 4305-4321.

The study of diseases in an evolutionary perspective helps us resolve key misconceptions about evolution and natural selection.

1. Natural selection does not operate to the same extent in all organisms or in all environments, but operates at various rates depending on the setting.

- Adaptations are not good or bad, but their evolutionary importance depends on the environment. A rapid environmental change, like the anthropogenic changes brought about by urban revolution, can cause disease phenotypes due to the change of the role of an adaptation that had been beneficial in a previous environment (**evolutionary mismatch**).
- Microorganisms (such as bacteria or viruses) evolve much faster than humans because they reproduce faster, their diversity evolves faster, and they are subject to natural selection pressures at a faster rate. Such rate differences are important both for the **evolution of the microbiome**, and for the **antagonistic evolutionary relationship** between human and pathogens.

Source commentary: *Section: Reasons why diseases exist*. Varki, A. (2012) Nothing in medicine makes sense, except in the light of evolution. *J. Mol. Med.* (2012) 90, 481-494.

The study of diseases in an evolutionary perspective helps us resolve key misconceptions about evolution and natural selection.

2. Natural selection does not have limitless possibilities for phenotype selection, but is subject to limitations, especially when genetic diversity of a population is poor.

- The available phenotypes in a population essentially represent **evolutionary compromises** between beneficial, neutral and unfavorable characteristics (traits) that have emerged in the evolutionary history of each species. For example, in human, genes that provided some **evolutionary advantage** have **coevolved** with genes promoting **susceptibility to diseases**.
- Natural selection acts on the genetic raw material available, i.e., on existing genetic variations. Thus, it can only operate on existing states and possibilities and cannot «revive» phenotypes that have been lost. For example, a decrease in the **microbiome diversity** reduces the chances of selection of important microbiota because of the loss of microbiota that are crucial for **regulation of immune response**.

Source commentary: *Section: Reasons why diseases exist*. Varki, A. (2012) Nothing in medicine makes sense, except in the light of evolution. *J. Mol. Med.* (2012) 90, 481-494.

The study of diseases in an evolutionary perspective helps us resolve key misconceptions about evolution and natural selection.

3. Natural selection does not act indiscriminately on any phenotype, but only on phenotypes that are linked to the reproductive success of the organisms.

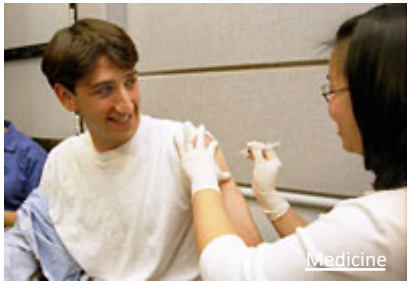
- Phenotypes that are «selected» in evolution through natural selection are linked ipso facto to the reproductive success and not to health, vigor or success of survival at old age. Characteristics that are associated to diseases of **ageing** might in fact provide **a selective advantage** at a younger, **reproductive age** (**angagonistic pleiotropy**).
- Phenotypes that are «selected» through natural selection usually have a cost that is outperformed by a more important benefit for survival at reproductive age. **Overresponsive reactions** that have evolved in human can cause unpleasant symptoms (anxiety, inflammation,ache, fever, nausea, diarrhea) but are useful **warning signs** that protect against more serious threats from dangerous pathological situations in the future (**smoke detector principle**).

Source commentary: *Section: Reasons why diseases exist*. Varki, A. (2012) Nothing in medicine makes sense, except in the light of evolution. *J. Mol. Med.* (2012) 90, 481-494.

Why is evolution important for humans today?

Understanding evolution helps us resolve biological matters that affect our life.

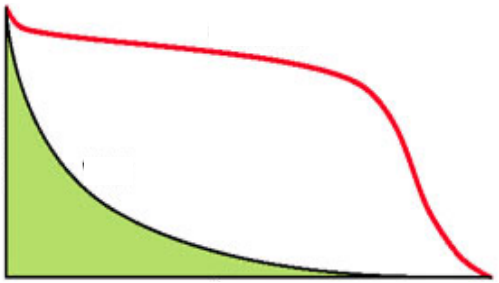
- **Importance of change:** new possibilities but also chances for adaptation in an ever-changing world.
- **Agricultural economy:** improving the resistance of agricultural crops to parasitic diseases, reinforced by an understanding of evolutionary relationships and genetic diversity.
- **Sustainable development:** preventing extinction conditions and conserving biodiversity by applying policies that take into consideration the relationship between population size and genetic diversity.
- **Modern Medicine:** improvement of prognosis, diagnosis and treatment of diseases, owing to an understanding of the evolution of microorganisms and of genes connected to modern-day diseases.



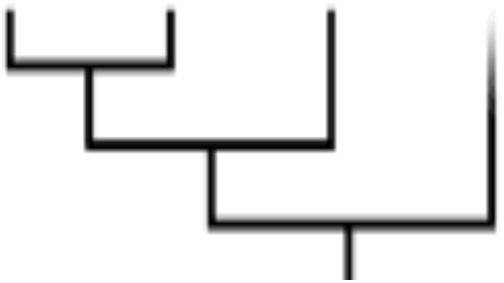
Relevance of evolution

Source of images on the right: The relevance of evolution (UC Museum of Paleontology) https://evolution.berkeley.edu/the-relevance-of-evolution

Why is Evolutionary Medicine important for humans today?



- It helps us understand the unified connection of human health evolution with the evolution of other organisms and the environment.
- It helps us understand the concepts of disease and the patient on a genetic basis of interdependence between human and the environment.
- It helps us understand the evolutionary value of other organisms and biodiversity for human health and well-being.
- It helps us design more effective and less intervening strategies for diagnosis and therapy.
- It allows us develop new themes of basic and biomedical research (such as, evolutionary perspective of ageing, evolutionary mismatch diseases, or the evolutionary relationship of microbiome with human).
- It helps us manage public health crises in efficient ways.



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