Viruses and Sars-Cov-2

Takeaway

1. **Viruses** are **part of us** (our world, our body)

2. Viruses are not bad or good, but their "behaviour" is driven by **evolution** and **human actions**

https://meet.google.com/hxw-nqia-pyc

Viruses and Sars-Cov-2

Takeaway

3. Viruses have accompanied us throughout **our entire evolutionary history**

4. Viruses have changed not only our **biology** but also the course of our **history**

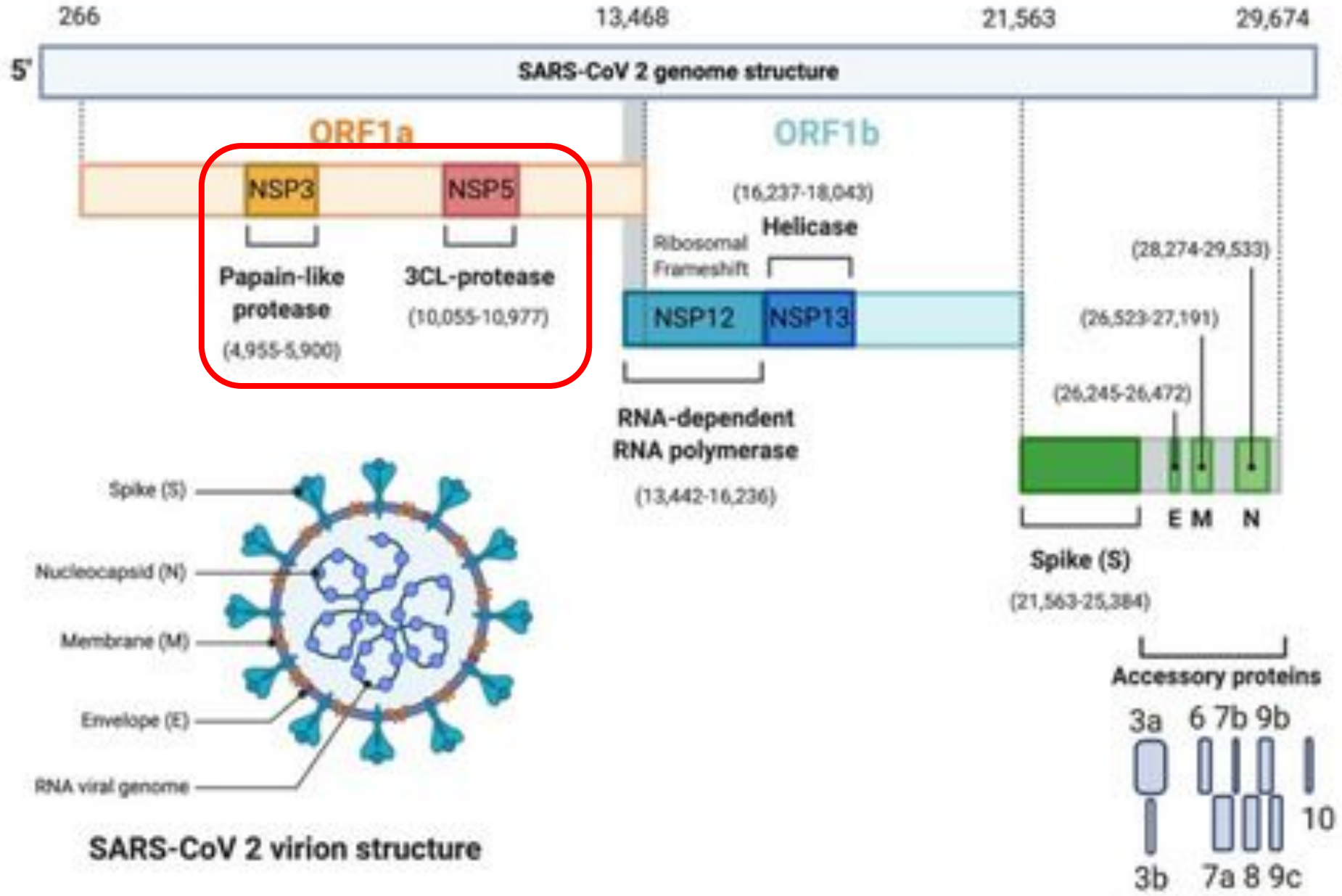
Viruses and Sars-Cov-2

Takeaway

5. Niche construction: Humans changed environment so as to increase viral burden

6. Viruses may be able to modify the human niche: Rabies virus and Covid-19

2019-nCOV (COVID-19)



Viruses: why are they important for us?

1. **Evolution**

As significant causes of morbidity and mortality, and in their capacity to act as "**molecular genetic parasites**" (Luria, 1959), viruses are in a strong position to **influence the evolution** of their hosts.

2. **Diversity**

Considering the speed with which new pathogens evolve (in general much faster than the host), it is in the best interests of the host **to be genetically diverse and highly mutable in the loci concerned with disease resistance**. Being isolated, then less diverse, may be harmful for humans (and favourable to viruses).

3. **Ecology**

Many of the pathogens that jump into people do so from rodents, bats, and non-human primates, likely due to some combination of these **species' abundance, proximity to people, and biological similarities to humans**.

nature immunology | VOL 23 | February 2022

SERIES | PERSPECTIVE

https://doi.org/10.1038/s41590-021-01030-z

Check for updates

A global effort to dissect the human genetic basis of resistance to SARS-CoV-2 infection

Evangelos Andreakos[1]✉, Laurent Abel[2,3,4], Donald C. Vinh[5,6], Elżbieta Kaja[7], Beth A. Drolet[8], Qian Zhang[2,3,4], Cliona O'Farrelly[9], Giuseppe Novelli[10], Carlos Rodríguez-Gallego[11,12], Filomeen Haerynck[13], Carolina Prando[14], Aurora Pujol[15,16,17], COVID Human Genetic Effort*, Helen C. Su[18], Jean-Laurent Casanova[2,3,4,19] and András N. Spaan[2,20]✉

SARS-CoV-2 infections display tremendous interindividual variability, ranging from asymptomatic infections to life-threatening disease. Inborn errors of, and autoantibodies directed against, type I interferons (IFNs) account for about 20% of critical COVID-19 cases among SARS-CoV-2-infected individuals. By contrast, the genetic and immunological determinants of resistance to infection per se remain unknown. Following the discovery that autosomal recessive deficiency in the DARC chemokine receptor confers resistance to *Plasmodium vivax*, autosomal recessive deficiencies of chemokine receptor 5 (CCR5) and the enzyme FUT2 were shown to underlie resistance to HIV-1 and noroviruses, respectively. Along the same lines, we propose a strategy for identifying, recruiting, and genetically analyzing individuals who are naturally resistant to SARS-CoV-2 infection.

https://www.nature.com/articles/s41590-021-01030-z.pdf

ACE2
ABO system
TMPRSS2
HLA

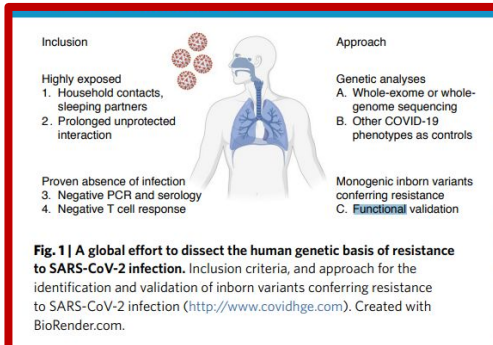
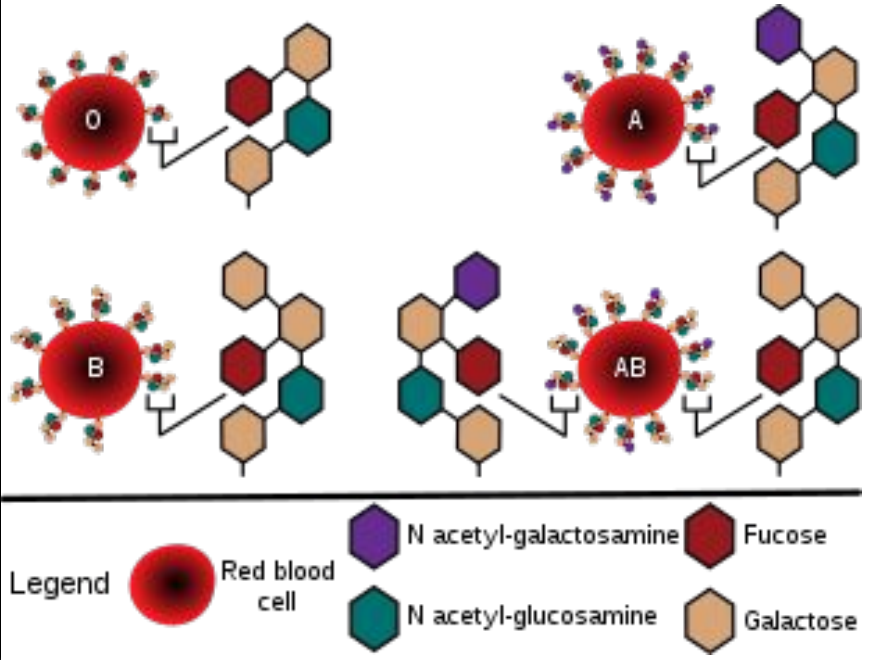


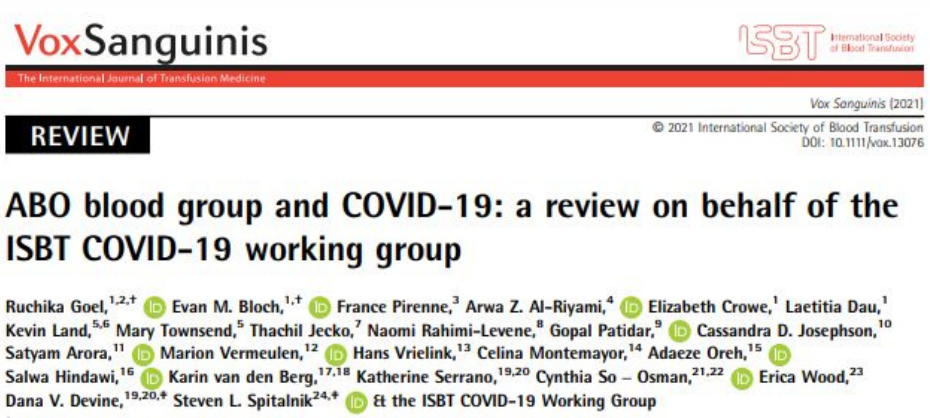
Fig. 1 | A global effort to dissect the human genetic basis of resistance to SARS-CoV-2 infection. Inclusion criteria, and approach for the identification and validation of inborn variants conferring resistance to SARS-CoV-2 infection (http://www.covidhge.com). Created with BioRender.com.

2019-nCOV (COVID-19) host genetic factors

ABO Blood group

	Group A	Group B	Group AB	Group O
Red blood cell type	A	B	AB	O
Antibodies in plasma	Anti-B	Anti-A	None	Anti-A and Anti-B
Antigens in red blood cell	A antigen	B antigen	A and B antigens	None





VoxSanguinis

The International Journal of Transfusion Medicine

ISBT International Society of Blood Transfusion

Vox Sanguinis (2021)

REVIEW

DOI: 10.1111/vox.13076

ABO blood group and COVID-19: a review on behalf of the ISBT COVID-19 working group

Ruchika Goel,[1,2,†] Evan M. Bloch,[1,†] France Pirenne,[3] Arwa Z. Al-Riyami,[4] Elizabeth Crowe,[1] Laetitia Dau,[1] Kevin Land,[5,6] Mary Townsend,[5] Thachil Jecko,[7] Naomi Rahimi-Levene,[8] Gopal Patidar,[9] Cassandra D. Josephson,[10] Satyam Arora,[11] Marion Vermeulen,[12] Hans Vrielink,[13] Celina Montemayor,[14] Adaeze Oreh,[15] Salwa Hindawi,[16] Karin van den Berg,[17,18] Katherine Serrano,[19,20] Cynthia So – Osman,[21,22] Erica Wood,[23] Dana V. Devine,[19,20,‡] Steven L. Spitalnik[24,‡] & the ISBT COVID-19 Working Group

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8014128/

Growing evidence suggests that ABO blood group may play a role in the immunopathogenesis of SARS-CoV-2 infection, with **group O individuals less likely to test positive and group A conferring a higher susceptibility to infection and propensity to severe disease.** *The protective effect of the O allele, however, is small, with an odds ratio of ~0.90*.

There are several hypotheses to explain the differences in SARS-CoV-2 infection by ABO type. For example, **anti-A and/or anti-B antibodies (e.g. present in group O individuals) could bind to corresponding antigens on the viral envelope and contribute to viral neutralization**, thereby preventing target cell infection. **The SARS-CoV-2 virus and SARS-CoV spike (S) proteins may be bound by anti-A isoagglutinins** (e.g. present in group O and group B individuals), which may block **interactions between virus and angiotensin-converting-enzyme-2-receptor,** thereby **preventing entry into lung epithelial cells**. ABO type-associated variations in angiotensin-converting enzyme-1 activity and levels of von Willebrand factor (VWF) and factor VIII could also influence adverse outcomes, notably in group A individuals who express high VWF levels.However, prospective and mechanistic studies are needed to verify several of the proposed associations.

2019-nCOV (COVID-19) host genetic factors

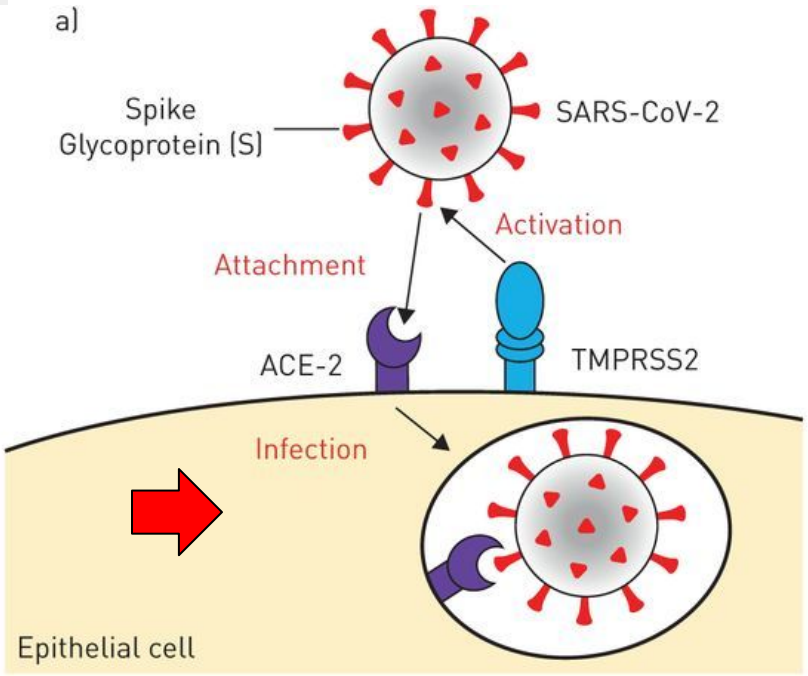
ABO Blood group

Group O people are more resistant to SARS-CoV because of ABO antibodies, whereas blood group A is related to a higher risk of getting COVID-19 as compared to non-A blood groups (B epidemiologic study in Wuhan and Shenzhen, China,J. Zhao et al., 2020).

These results are in line with earlier reported investigations in the Hong Kong outbreak. The authors find that Group O people are quite resistant to infection and can decline the infection rate in the population (Guillon et al., 2008). The ABO histo-blood group comprises two antigens (A and B antigens), which are the ABO gene product. Group O people express the H antigen, the biosynthetic precursor to A and B antigens. Besides red cells, numerous and secretions, such as endothelium, intestinal mucosa, heart, kidney, as well as other organs, express ABH antigens. ABH is a carbohydrate antigen expressed on glycoproteins and glycosphingolipids (GSLs; Cooling, 2015). Glycan analysis of SARS-CoV S protein reveals a broad range of structures, such as complex N-glycans with 2–4 antennae able to support ABH epitopes (Y. Cheng et al., 2005). It is highly probable that on the S protein and host envelope GSLs, most human isolates express ABH antigens since the virus targets respiratory and gastrointestinal mucosa. Monoclonal anti-A and human anti-A may block S protein-expressing A antigen (Guillon et al., 2008).

2019-nCOV (COVID-19) host genetic factors

DOI: 10.1002/jcp.29868

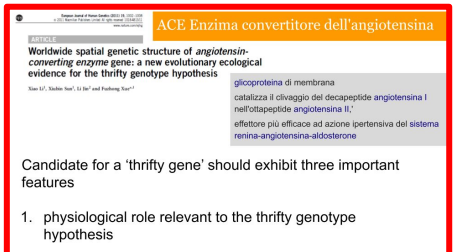


SARS-CoV-2 binding to the angiotensin-converting enzyme 2 (**ACE-2**) receptor following activation of the spike protein (s) by transmembrane serine protease 2 (**TMPRSS2**), which leads to endocytosis and infection.

ACE2

Angiotensin-converting **enzyme** 2

- Xp22.22, 41.04 kb long, 18 or 19 exons
- zinc-containing metalloenzyme attached to the cell membranes of cells located in the lungs, arteries, heart, kidney, and intestines.
- lowers blood pressure by catalyzing the hydrolysis of angiotensin II (a vasoconstrictor peptide) into angiotensin (a vasodilator).
- entry point into cells for some coronaviruses, including HCoV-NL63, SARS-CoV, and SARS-CoV-2.

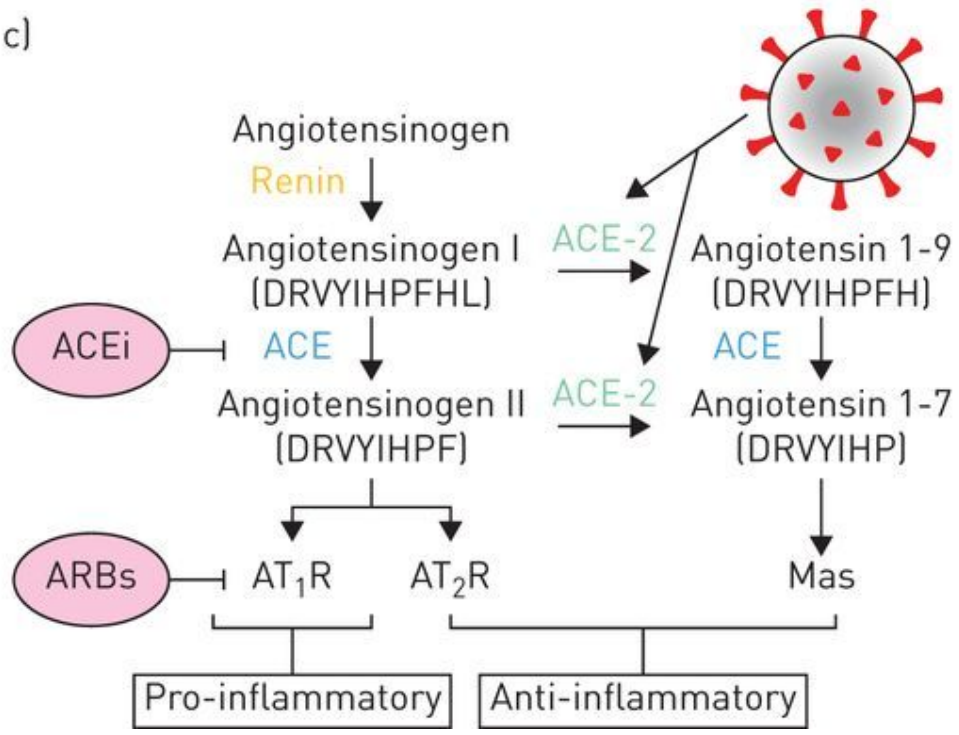


2019-nCOV (COVID-19) host genetic factors

DOI: 10.1002/jcp.29868

Upon SARS-CoV-2 binding to ACE-2, there is a shift in the ACE/ACE-2 balance towards a predominance of ACE, resulting in increased pro-inflammatory effects and tissue damage.

The generation of angiotensin II induces vasoconstriction of blood vessels and pro-inflammatory effects through the binding of angiotensin II receptor type 1 (AT1R), while the receptor type 2 (AT2R) may negatively regulate this pathway.



ACE-2 inhibits the activity of angiotensin II by converting angiotensin I to angiotensin 1–9 and angiotensin II to angiotensin 1–7, which binds to the MAS1 proto-oncogene (Mas) receptor with anti-inflammatory effects.

https://doi.org/10.1101/2020.04.07.024752

Human ACE2 receptor polymorphisms predict SARS-CoV-2 susceptibility

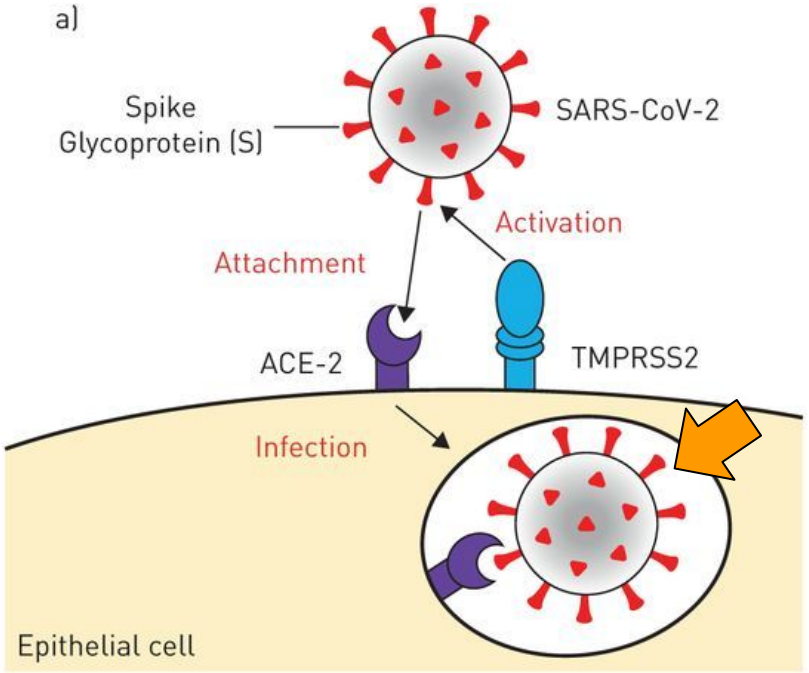
Eric W. Stawiski[1*], Devan Diwanji[2,3*], Kushal Suryamohan[1*], Ravi Gupta[4], Frederic A. Fellouse[5], J. Fah Sathirapongsasuti[1], Jiang Liu[6], Ying-Ping Jiang[6], Aakrosh Ratan[7,8],

Analysis of several large **genomic datasets** that included over 2**90,000 samples representing >400 population groups** identified **multiple ACE2 protein-altering variants, some of which mapped to the S-protein-interacting ACE2 surface**. Using recently reported structural data and a recent S-protein interacting synthetic mutant map of ACE2, we have identified natural ACE2 variants that are predicted to alter the virus-host interaction and thereby potentially alter host susceptibility. In particular, human **ACE2 variants S19P, I21V, E23K, K26R, T27A, N64K, T92I, Q102P and H378R are predicted to increase susceptibility.** The T92I variant, part of a consensus NxS/T N-glycosylation motif, confirmed the role of N90 glycosylation in immunity from non-human CoVs. **Other ACE2 variants K31R, N33I, H34R, E35K, E37K, D38V, Y50F, N51S, M62V, K68E, F72V, Y83H, G326E, G352V, D355N, Q388L and D509Y are putative protective variants predicted to show decreased binding to SARS-CoV-2 S-protein.** Overall, **ACE2 variants are rare**, consistent with the lack of selection pressure given the recent history of SARS-CoV epidemics, however, are likely to play an important role in altering susceptibility to CoVs.

2019-nCOV (COVID-19) host genetic factors

10.1093/infdis/jiv246

https://www.aging-us.com/article/103415/pdf



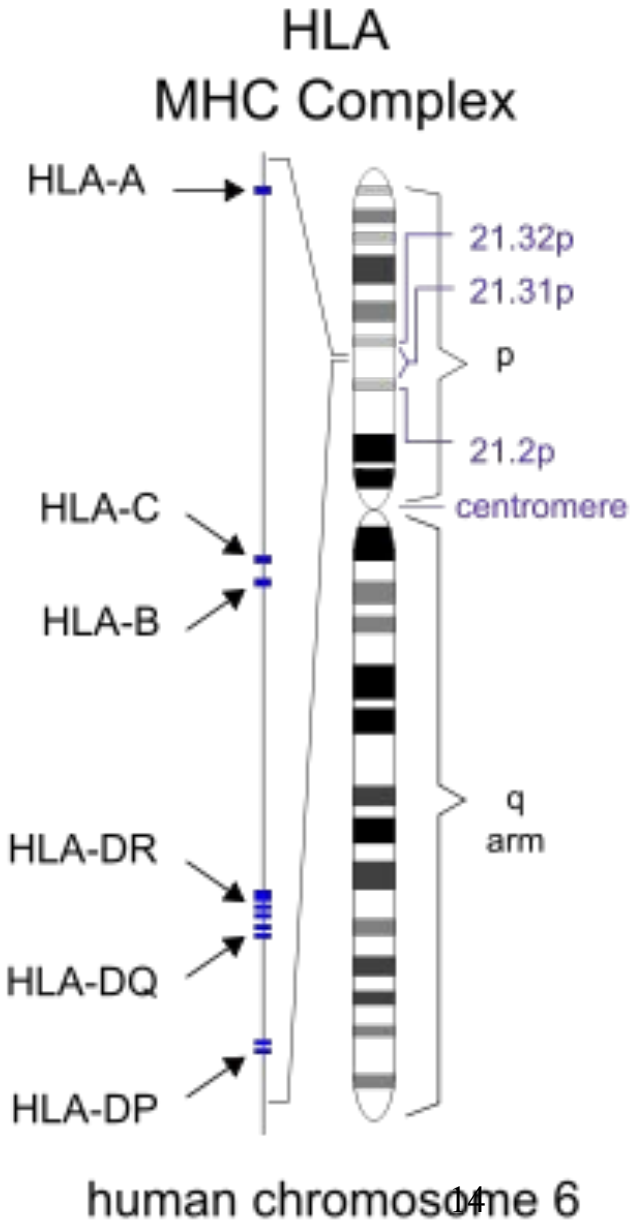
Transmembrane protease serine-type 2 (TMPRSS2)

- chr **21q22**.
- type II transmembrane serine protease family
- SARS-CoV-1, MERS-CoV, and SARS-CoV-2 are activated by TMPRSS2 and can thus be inhibited by TMPRSS2 inhibitors
- in SARS-Cov-2 the spike protein is activated by TMPRSS2 to induce virus-cell membrane fusion at the cell surface, and also coronaviruses entry into the host cell is facilitated by TMPRSS2
- Two single-nucleotide polymorphisms (SNPs; rs2070788 and rs383510) are related to increased TMPRSS2 gene expression and are connected significantly to the susceptibility to H7N9 influenza
- rare alleles of these haplotypes, all predicted to induce higher levels of *TMPRSS2*, are more frequent in the Italian than in the East Asian population.> mortality?

2019-nCOV (COVID-19) host genetic factors

Human leukocyte antigen (HLA)

- group of related proteins encoded by the major histocompatibility complex (MHC) gene complex
- responsible for the regulation of the immune system.
- HLA genes are highly polymorphic, allowing them to fine-tune the adaptive immune system
- MHC class I loci (A, B, and C), all of which are the HLA Class1 group present peptides from inside the cell; **if the cell is infected by a virus, the HLA system brings fragments of the virus to the surface of the cell so that the cell can be destroyed by the immune system.**
- SARS-CoV-2-related antigen epitopes are all more or less associated with HLA antigen recognition, as inferred by known SARS-CoV-2 gene and protein sequences, a close association between a COVID-19 pandemic and the HLA system is hypothesized

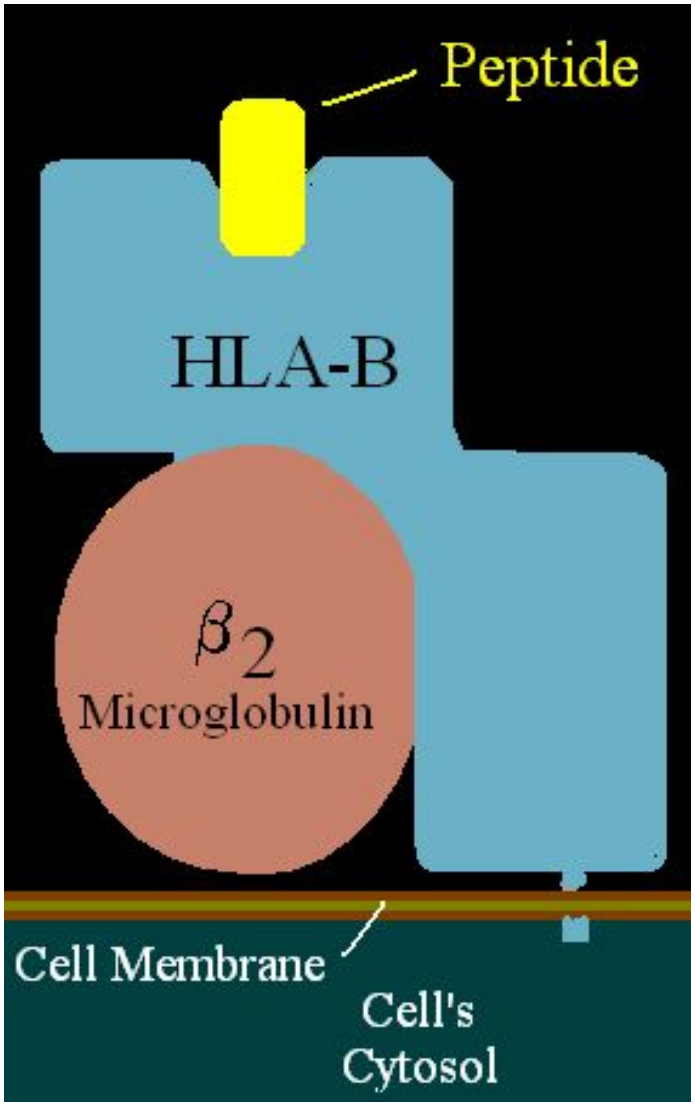


2019-nCOV (COVID-19) host genetic factors

10.1093/infdis/jiv246

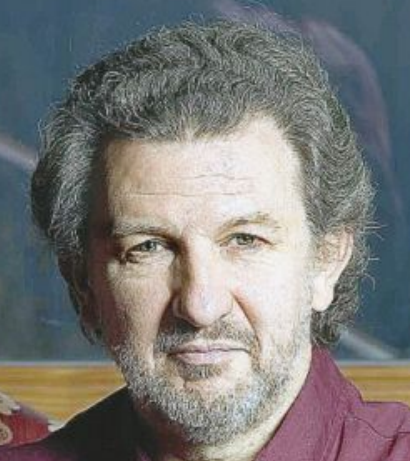
Human leukocyte antigen (HLA)

- Silico analysis revealed that HLA-B*46:01 has the least number of peptides binding site for SARS-CoV-2) >susceptible to COVID-19)
- HLA-B*1503 can present the SARS-CoV-2 peptides that are very conserved and common among human coronaviruses with greatest capability; may allow cross-protective T-cell-based immunity
- Polypeptides typically 7-11 amino acids in length, originate from proteins being expressed by the cell (self and non-self). Cytotoxic T cells "read" the peptide presented by the complex, normally binding to non-self peptides starting a series of events is initiated culminated in cell death via apoptosis



Perchè parlare ancora di razze...

Struttura geografica della diversità genetica, farmacogenetica, medicina di precisione



Dizionario della stupidità. Fenomenologia del non-senso della vita

I geni del ► politicamente corretto hanno invece deciso che il modo più semplice e spiccio per eliminare la discriminazione razziale sia cancellare la parola «razza» dal vocabolario. Ma poiché i geni della biologia non si sono ancora adeguati, i figli di genitori bianchi continuano imperterriti a nascere bianchi, e analogamente per gli altri colori, a testimonianza della natura genetica delle varie razze umane.

Lo stesso succede per le razze canine o bovine, ma per fortuna nessuno ha (ancora) proposto di parlare di "etnia" chihuahua o chianina. E poiché le cose continuano a esistere anche se gli struzzi mettono la testa sotto terra, i Padri Costituenti sono stati sensati a sottolineare che ci sono sia i sessi sia le razze, ma che questo non giustifica né il sessismo contro le ► donne, né il razzismo contro le razze.

Cosa sono le **razze**

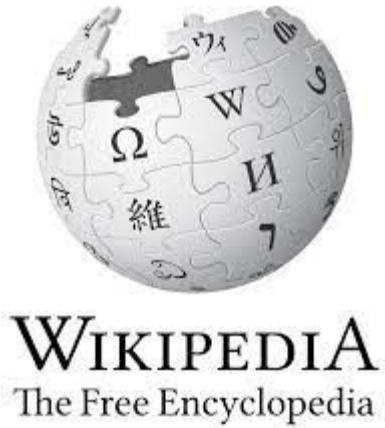
Esistono in **natura**

Descrivono la **diversità umana**

...Razza, parola equina

selezione artificiale!

selezione naturale



A **race** is a grouping of humans based on shared physical or social qualities into categories generally viewed as distinct by society.[1]

Cosa sono le **razze*** =

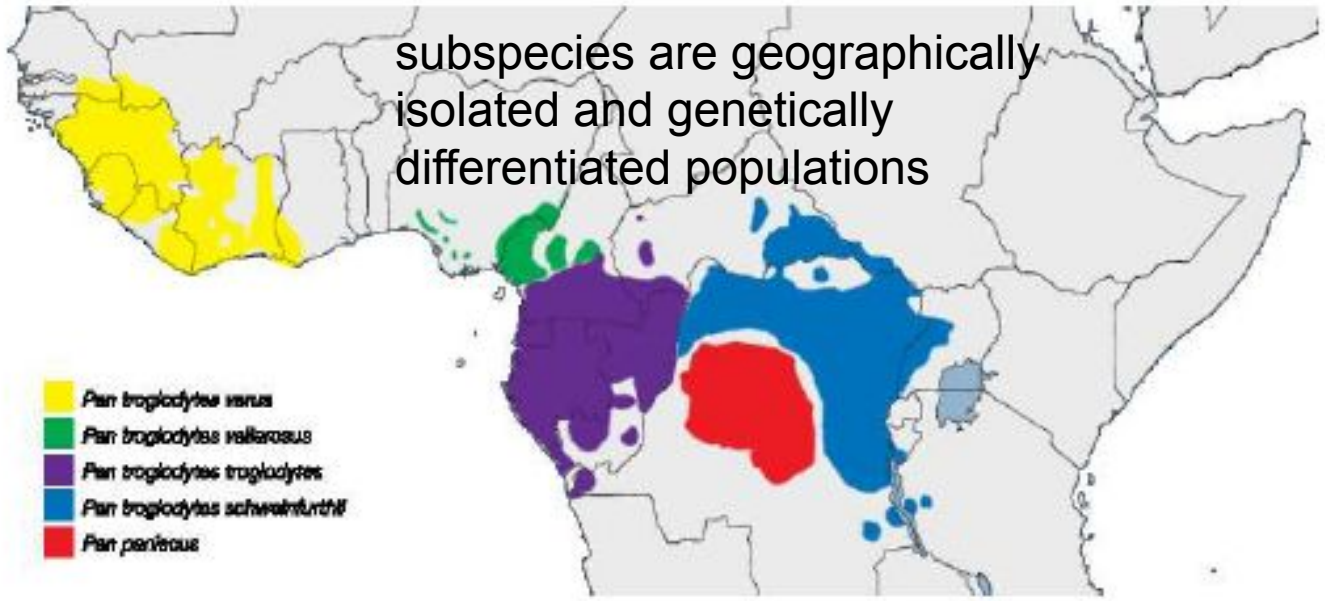
Non sono un sinonimo di diversità

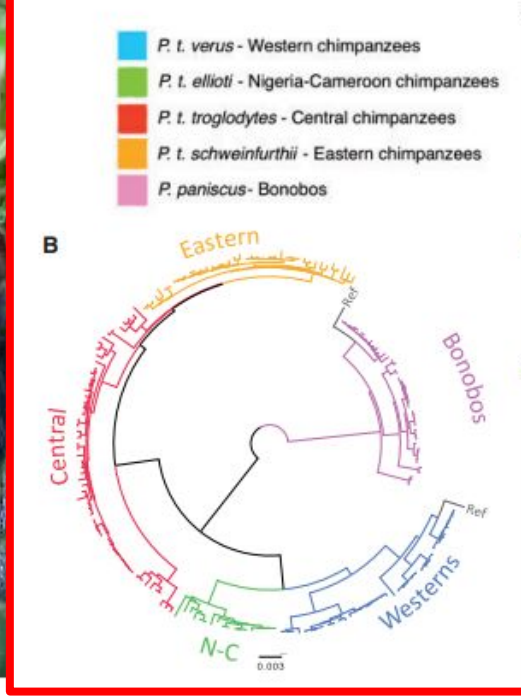
unità

- discrete
- esclusive
- omogenee

*sottospecie

Esistono in **natura!**





GBE

Demographic History of the Genus *Pan* Inferred from Whole Mitochondrial Genome Reconstructions

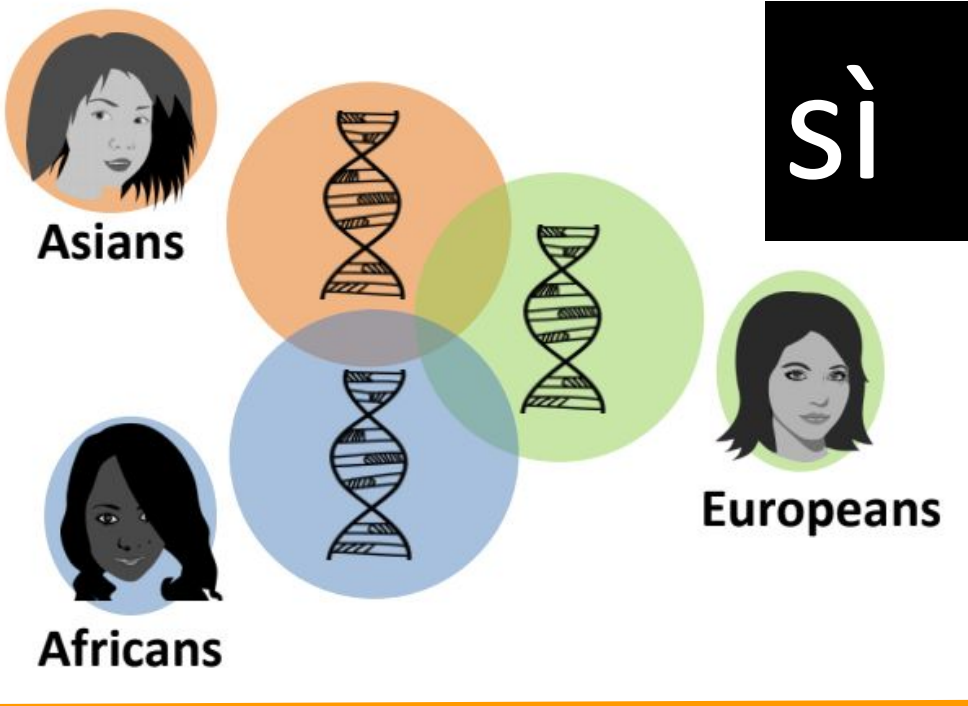
Irene Lobon[1,#], Serena Tucci[2,#], Marc de Manuel[1], Silvia Ghirotto[2], Andrea Benazzo[2], Javier Prado-Martinez[3], Belen Lorente-Galdos[4], Kiwoong Nam[5], Marc Dabad[7,8], Jessica Hernandez-Rodriguez[1], David Comas[1], Arcadi Navarro[1,6,7], Mikkel H. Schierup[5], Aida M. Andres[9], Guido Barbujani[2], Christina Hvilsom[10], and Tomas Marques-Bonet[1,6,7,*]

Abstract

The genus *Pan* is the closest genus to our own and it includes two sp
The later is constituted by four subspecies, all highly endangered. Th
intricate relationship among subspecies and the statistical limitation
analyzed. Here, we present a new method to reconstruct comple
shotgun (WGS) datasets, mtArchitect, showing that its reconstru
mitogenomes. We used this approach to build the mitochondrial genomes of 20 newly sequenced samples which, together with available genomes, allowed us to analyze the hitherto most complete *Pan* mitochondrial genome dataset including 156 chimpanzee and 44 bonobo individuals, with a proportional contribution from all chimpanzee subspecies. We estimated the separation time between chimpanzees and bonobos around 1.15 million years ago (Mya) [0.81–1.49]. Further, we found that under the most probable genealogical model the two clades of chimpanzees, Western + Nigeria-Cameroon and Central + Eastern, separated at 0.59 Mya [0.41–0.78] with further internal separations at 0.32 Mya [0.22–0.43] and 0.16 Mya [0.17–0.34], respectively. Finally, for a subset of our samples, we compared nuclear versus mitochondrial genomes and we found that chimpanzee subspecies have different patterns of nuclear and mitochondrial diversity, which could be a result of either processes affecting the mitochondrial genome, such as hitchhiking or background selection, or a result of populatio

https://academic.oup.com/gbe/article/8/6/2020/2574100

Esistono unità discrete, esclusive ed omogenee sulla base del DNA?



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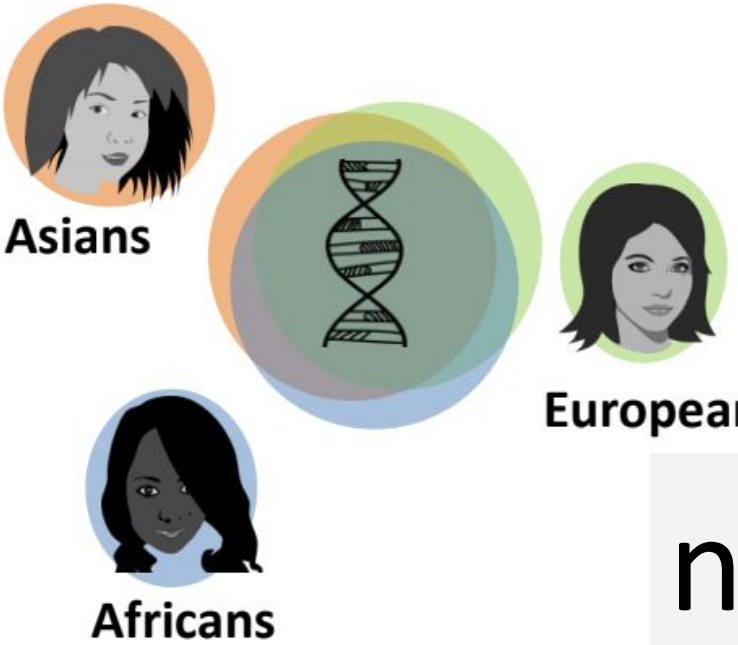
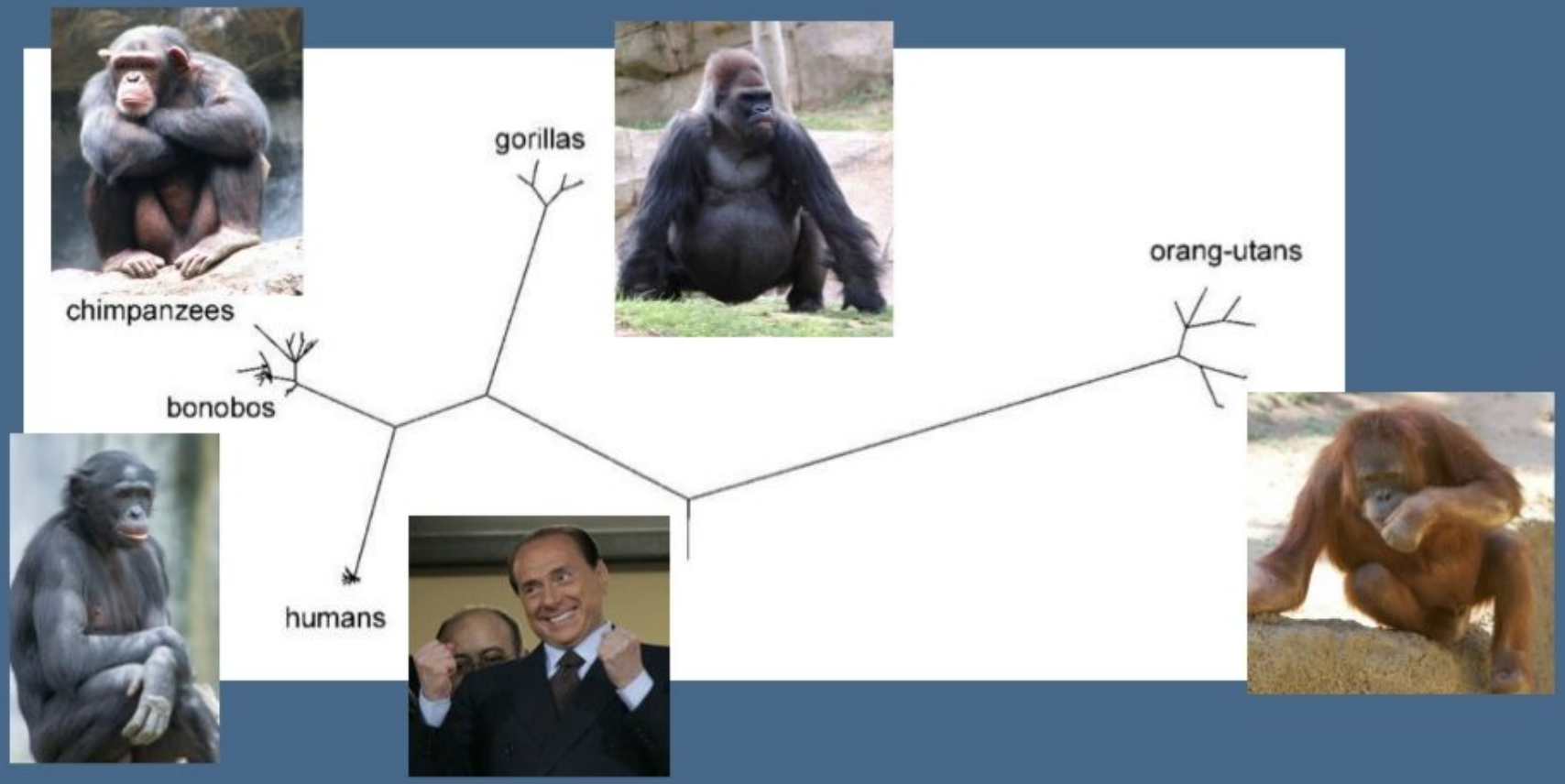


no

Riassunto delle (3) puntate precedenti

1 Extent of diversity compared



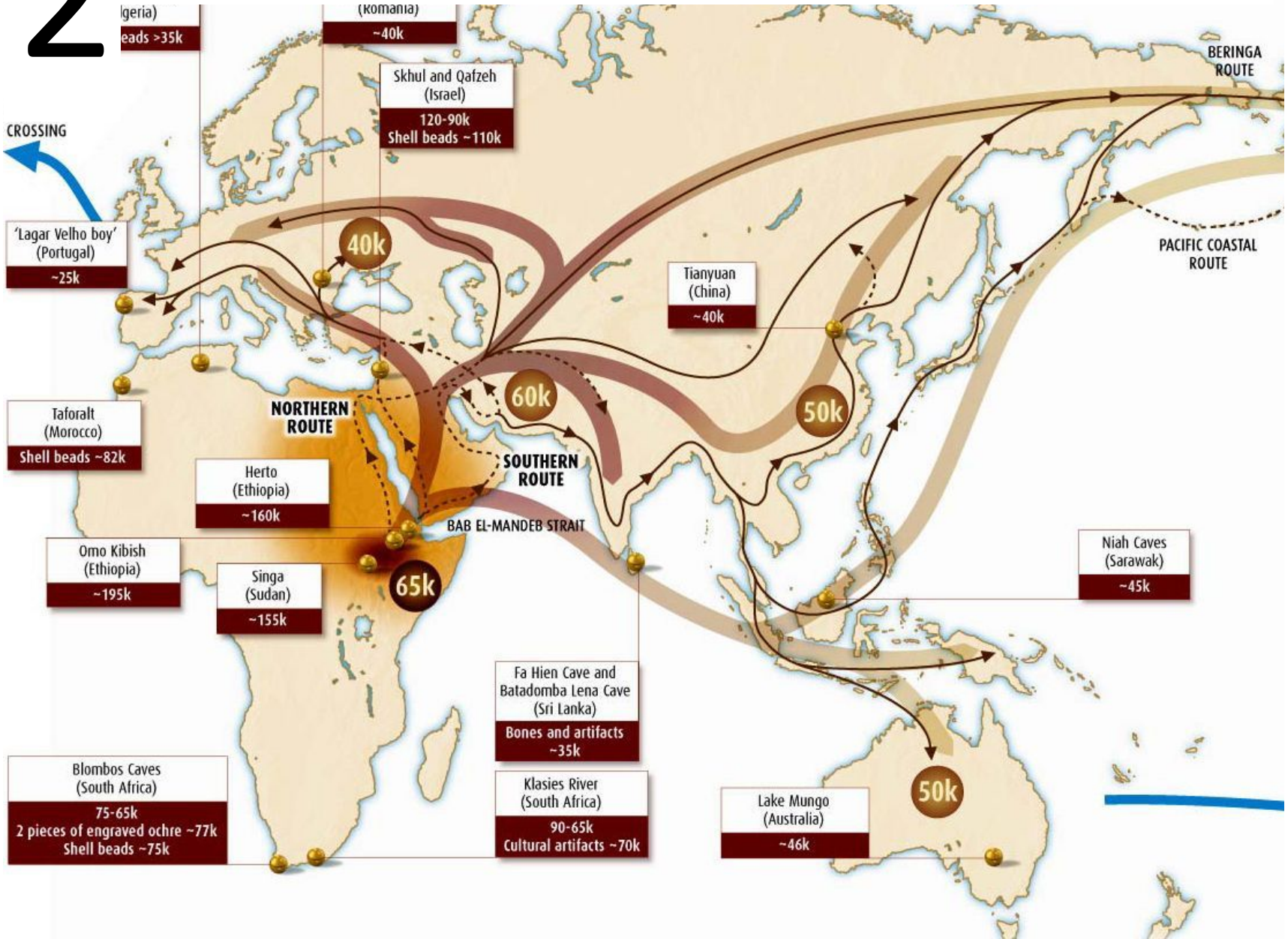
Phylogenetic tree of human (n=70), chimpanzee (n=30), bonobo (n=5), gorilla (n=11) and orang-utan (n=14), based on 10,000 bp sequences of a noncoding Xq13.3 region. Kaessmann et al. (2001).

1 Extent of diversity compared

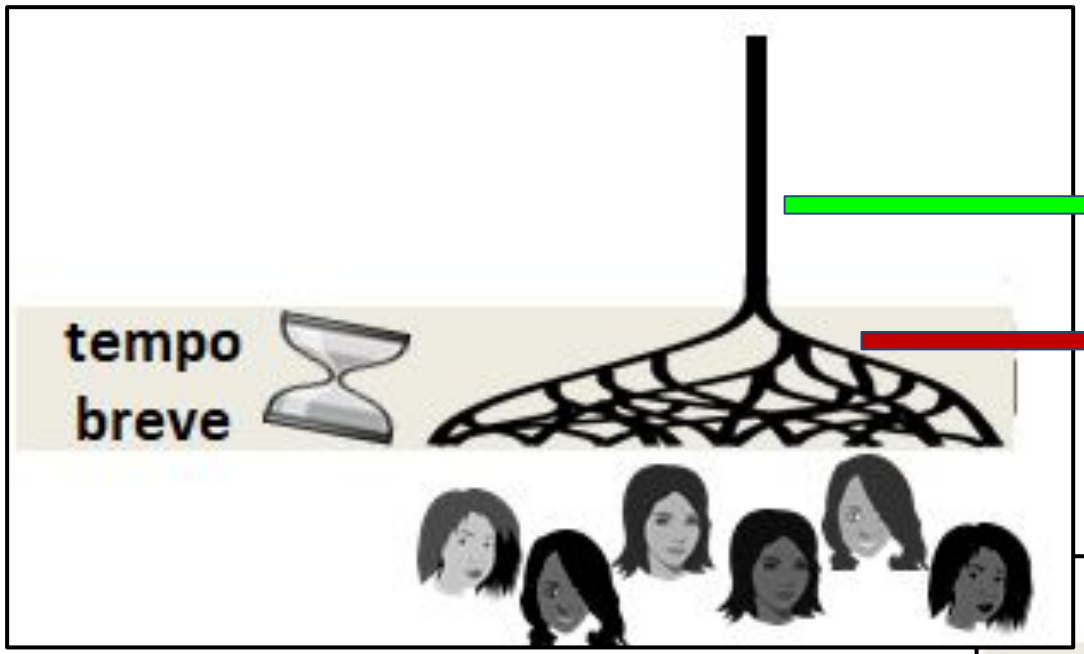
TABLE 7. 3: RELATIVE DIVERSITIES OF VARIOUS LOCI IN HUM

Locus	Chimpanzee vs. human	Bonobo vs. human
Xq13.3	3-fold greater	n.d.
mtDNA	3–4-fold greater	Greater
Y chromosome	Greater	n.d.
MHC class I genes	Greater, but less in HLA-A comparison	n.d.
ABO blood group genes	2–3-fold less	4–7-fold less
Microsatellites	Less	n.d.
Minisatellites	Less	n.d.

2 Time since divergence



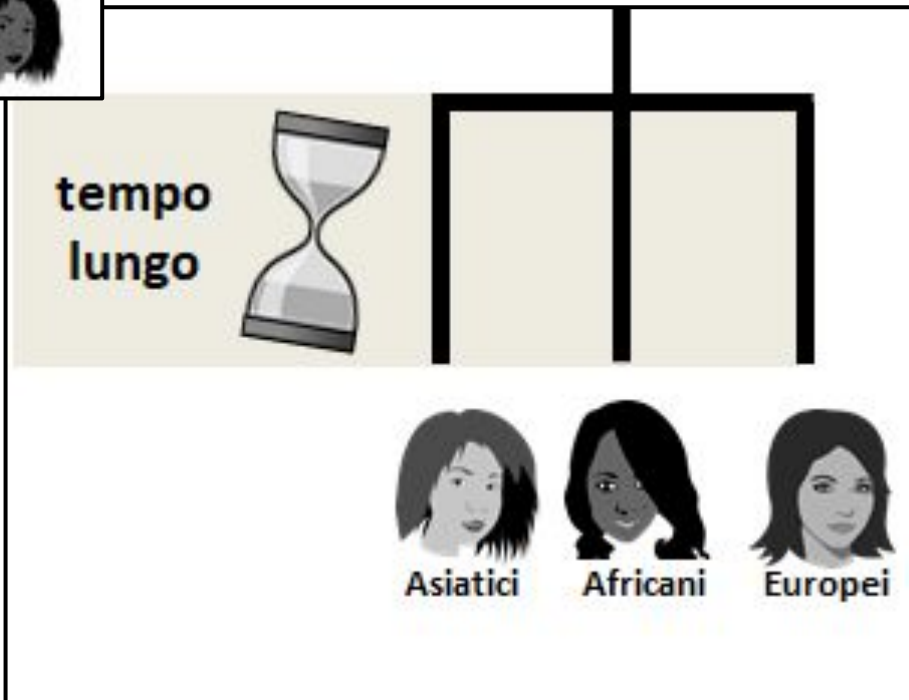
and 44 bonobo individuals, with a proportional contribution from all chimpanzee subspecies. We estimated the separation time between chimpanzees and bonobos around 1.15 million years ago (Mya) [0.81–1.49]. Further, we found that under the most



230 KYA
H. sapiens emergence

65 KYA
H. sapiens expansion

2 Time since divergence



3 Genetic distances among subgroups

Current Biology 16, 1133–1138, June 6, 2006 ©2006 Elsevier Ltd All rights reserved DOI 10

Demographic History and Genetic Differentiation in Apes

https://www.cell.com/current-biology/pdf/S0960-9822(06)01494-1.pdf

Multiple intergenic autosomal regions totaling 22,400 base pairs (bp) in 20 individuals each from western, central, and eastern chimpanzee groups and in 18 bonobos, and 16,000 bp in 10 Bornean and 12 Sumatran orangutans. For human pops. 30 individuals. These regions are analyzed together with homologous information from three human populations and gorillas.

Table 2. F_{st} and π_b Values, above and below the Diagonal, Respectively, for Each Pairwise Comparison

π between (%) \ F_{st}		Bonobos	Chimpanzees			Humans			Gorillas	Orangs	
		Bonobos	Central	Eastern	Western	Hausa	Chinese	Italians	Gorillas	Sumatran	Bornean
Bonobos	Bonobos		0.49	0.54	0.68	0.93			0.93	0.93	
Chimpanzees	Central	0.32		0.09	0.29	0.89			0.89	0.91	
	Eastern	0.31	0.20		0.32						
	Western	0.32	0.21	0.20							
Humans	Hausa	1.12	1.19				0.15	0.14	0.92	0.94	
	Chinese					0.13		0.09			
	Italians					0.14	0.09				
Gorillas	Gorillas	1.55	1.53			1.54				0.93	
Orangs	Sumatran	3.02	3.09			3.19			3.15		0.28
	Bornean									0.41	

3

Genomic estimates of F_{ST} for the global human population are ~ 0.12

N of markers	Samples	F_{ST}	Reference
599,356 SNPs	209 individuals from 4 populations: Caucasian, Chinese, Japanese, Yoruba	**0.13**	Weir et al. 2005
1,034,741 SNPs	71 individuals from 4 populations: Caucasian, Chinese, Japanese, Yoruba	**0.10**	Weir et al. 2005
1,007,329 SNPs	269 individuals from 4 populations: Caucasian, Chinese, Japanese, Yoruba	**0.12**	International HapMap Consortium 2005
443,434 SNPs	3845 worldwide distributed individuals	**0.052**	Auton et al. 2009
2,841,354 SNPs	210 individuals from 4 populations: Caucasian, Chinese, Japanese, Yoruba	**0.11**	Barreiro et al. 2008
243,855 SNPs	554 individuals from 27 worldwide populations	**0.123**	Xing et al. 2009
100 Alu insertions	710 individuals from 23 worldwide populations	**0.095**	Watkins et al. 2008
67 CNVs	270 individuals from 4 populations with ancestry in Europe, Africa or Asia	**0.11**	Redon et al. 2006

Human populations display ~ 12% of the maximum

Mind the numbers

Humans and chimps share >98% of their genomes

Among the 2% differences, 1.9% are fixed differences within species

The remaining fraction, 0.1%, contains all human genomic variation

oppure

Due persone prese a caso nel mondo hanno il 99.9% di nucleotidi identici nel loro DNA

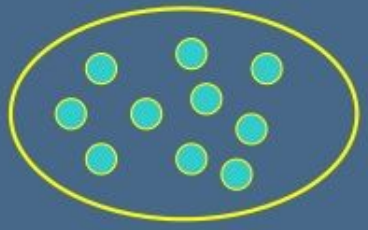
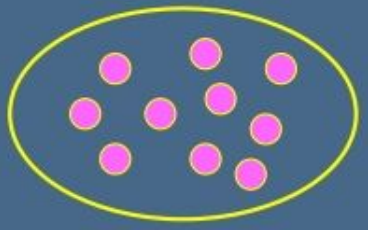
International HapMap Consortium 2006

Come si ripartisce questo 0.1% di **diversità totale**

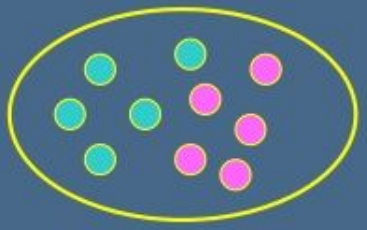
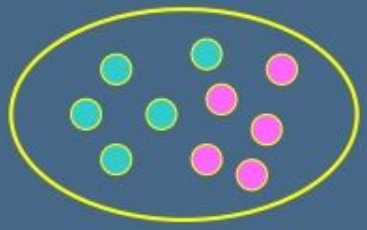
- dentro le popolazioni
- tra le popolazioni
- tra i gruppi di popolazioni (continenti, “razze”)

Genetic variances within and between populations

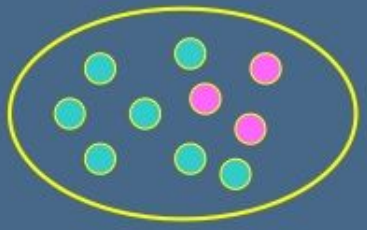
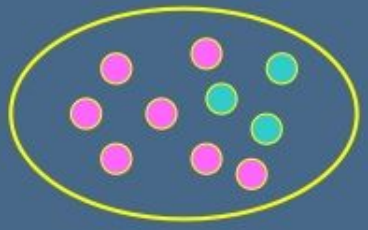
Population 1 | Population 2 | variance between pops.

100%

0%

19%

Studi indipendenti della variabilità umana portano a risultati quasi identici: 85, 5, 10

Lewontin (1972)	17 loci	85%	8%	6%
Latter (1973)	18	86%	5%	9%
Barbujani et al. (1997)	109	85%	5%	10%
Jorde et al. (2000)	100	85%	2%	13%
Romualdi et al. (2002)	32	83%	8%	9%
Rosenberg et al. (2002)	377	93%	3%	4%
Excoffier & Hamilton (2003)	377	88%	3%	9%
Ramachandran et al. (2005)	17	90%	5%	5%
Bastos-Rodriguez et al. (2006)	40	86%	2%	12%
Li et al. (2008)	650 000	89%	2%	9%

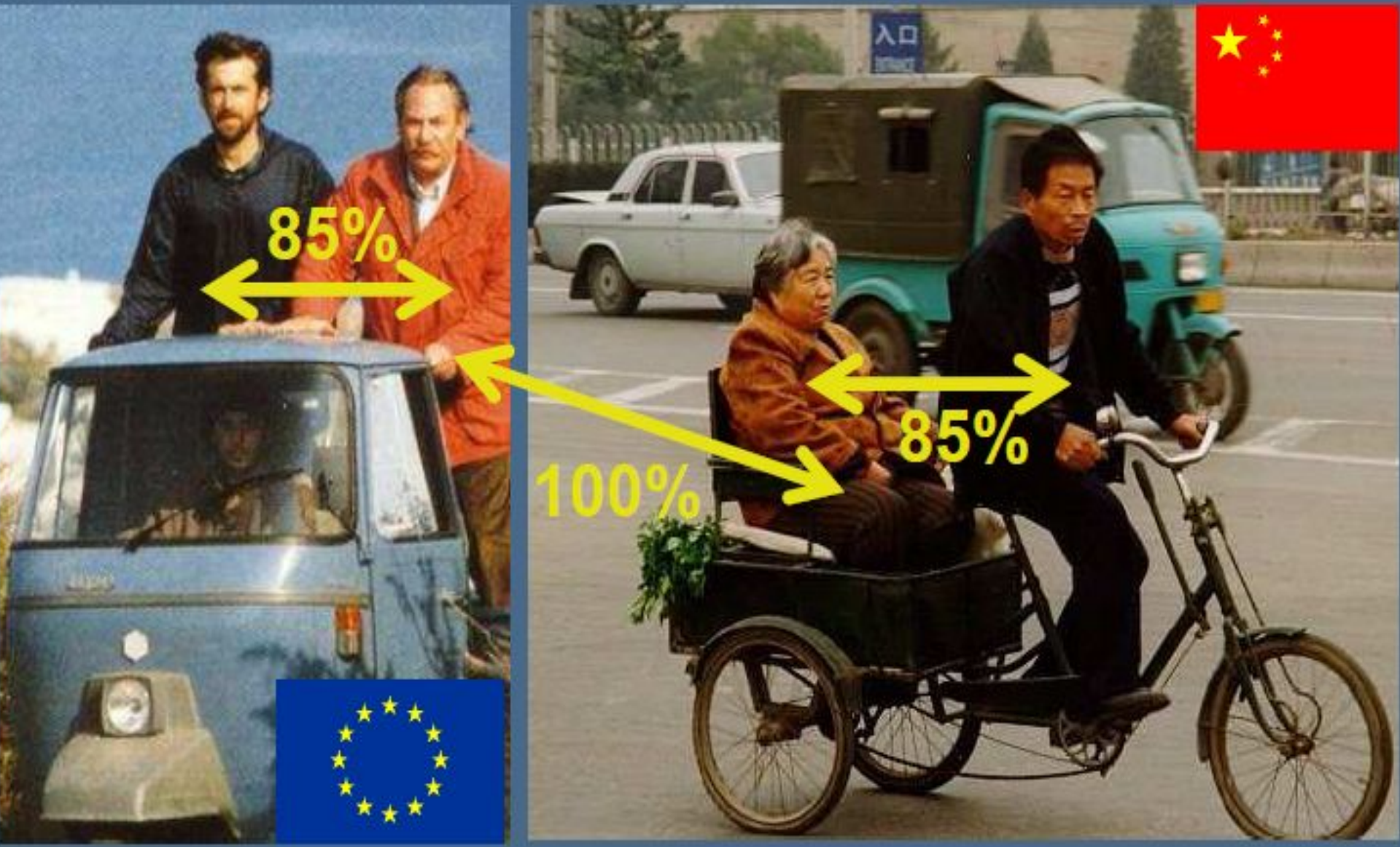
85% 5% 10%

entro popolazioni

fra popolazioni

fra razze o continenti

I membri della nostra comunità sono solo di poco più simili a noi della gente di Paesi lontani



Quindi la diversità tra i gruppi di popolazioni

1/1.000 * 1/10 = 1/10.000

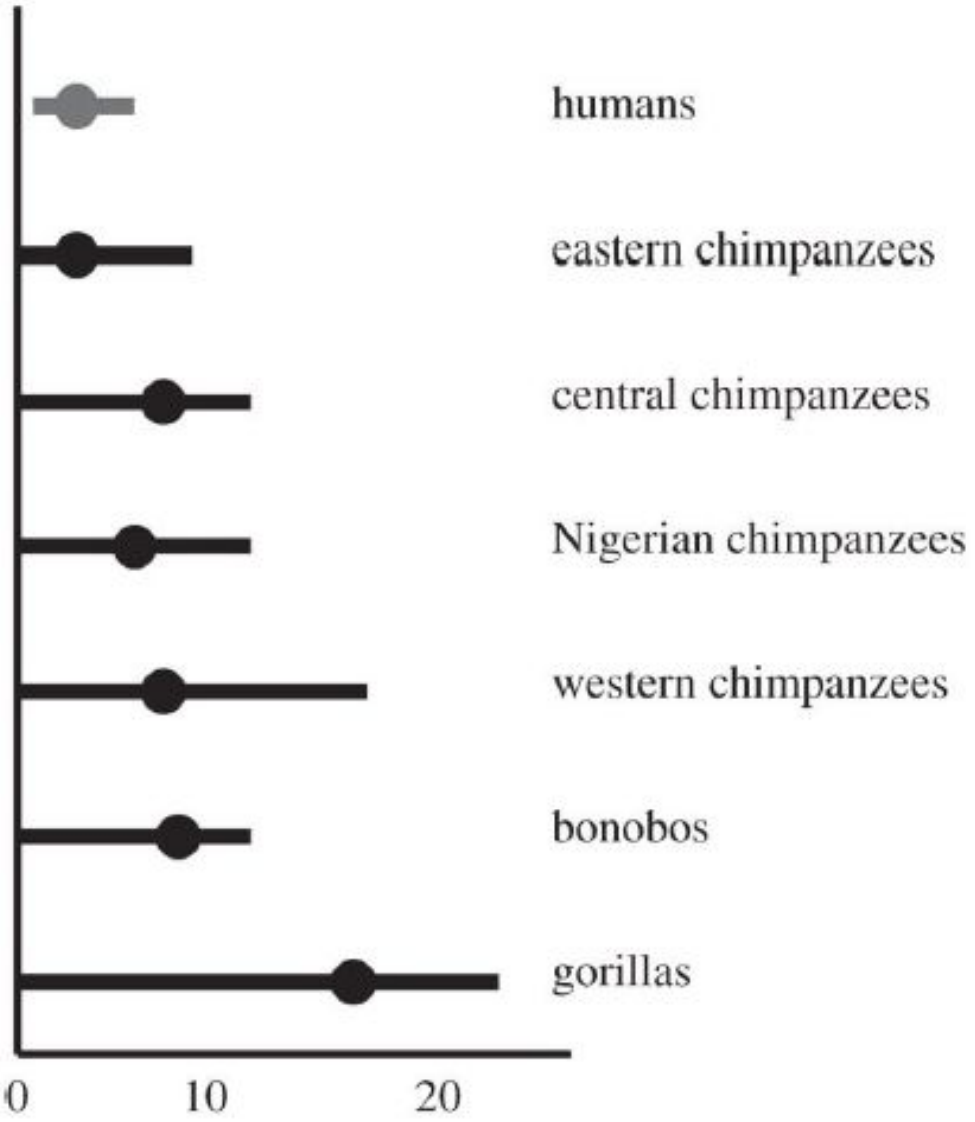
Gene Identification Method	EST Alignment	Predicted	mRNA Alignment
Number of Genes	3,295	11,972	17,708
Exons/Gene (Avg)	4	5	12
Exon Length (Avg)	440	158	226
Intron Length (Avg)	5,605	10,512	5,478
mRNA Length (Avg)	2,127	820	2,741
Gene Length (Avg)	13,940	43,918	55,147

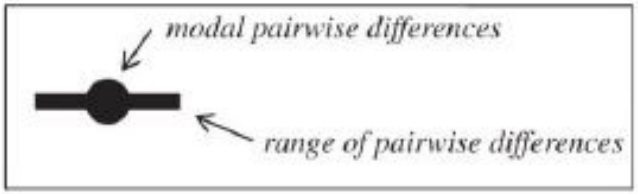
Ma la partita non è ancora chiusa

La 1/10.000 parte di 3.200.000.000 è 300.000 nucleotidi

Troviamo nei 300KB segni coerenti di differenziazione in razze?

La variabilità genetica della nostra specie è...

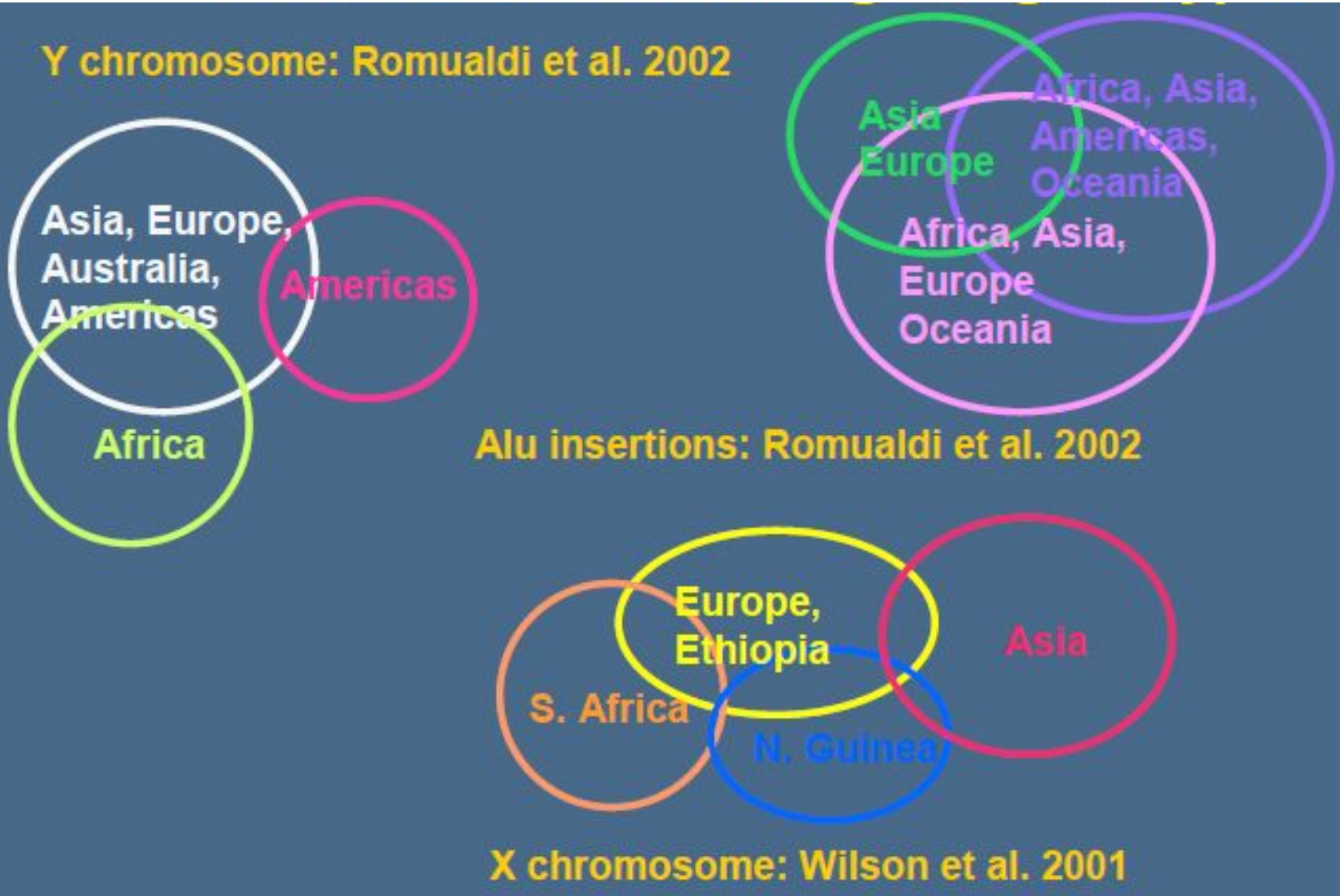




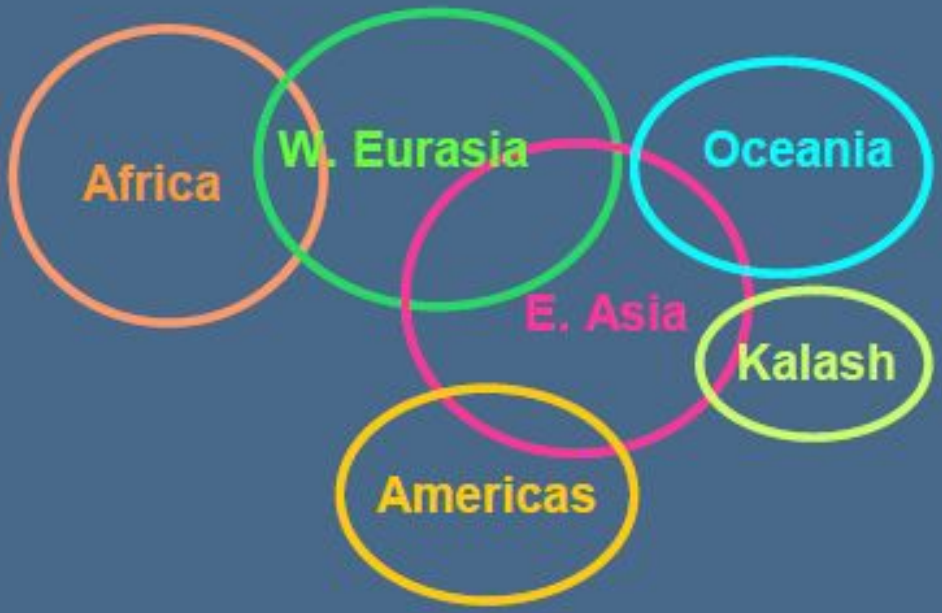
Foley R A , Mirazón Lahr M Phil. Trans. R. Soc. B 2011;366:1080-1089

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

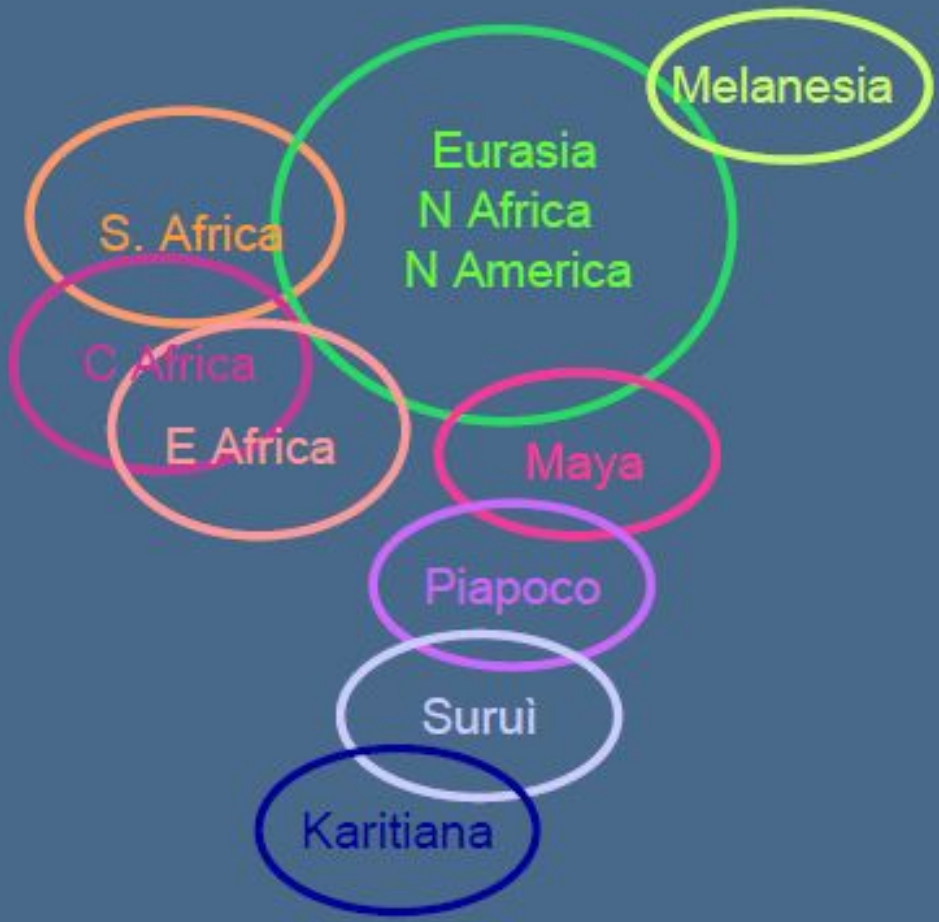
Evidenze genetiche di raggruppamenti razziali ?



Genes, as well as morphology, suggest inconsistent clusterings of genotypes



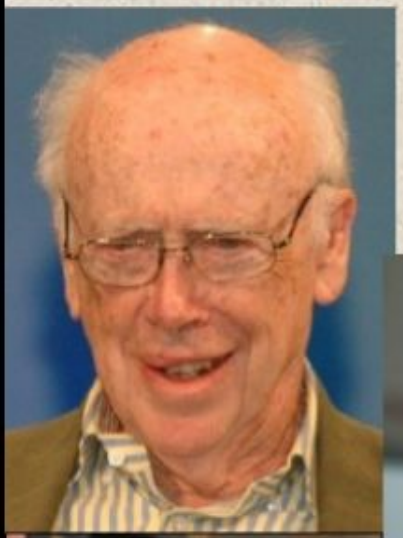
377 STR loci: Rosenberg et al. 2005

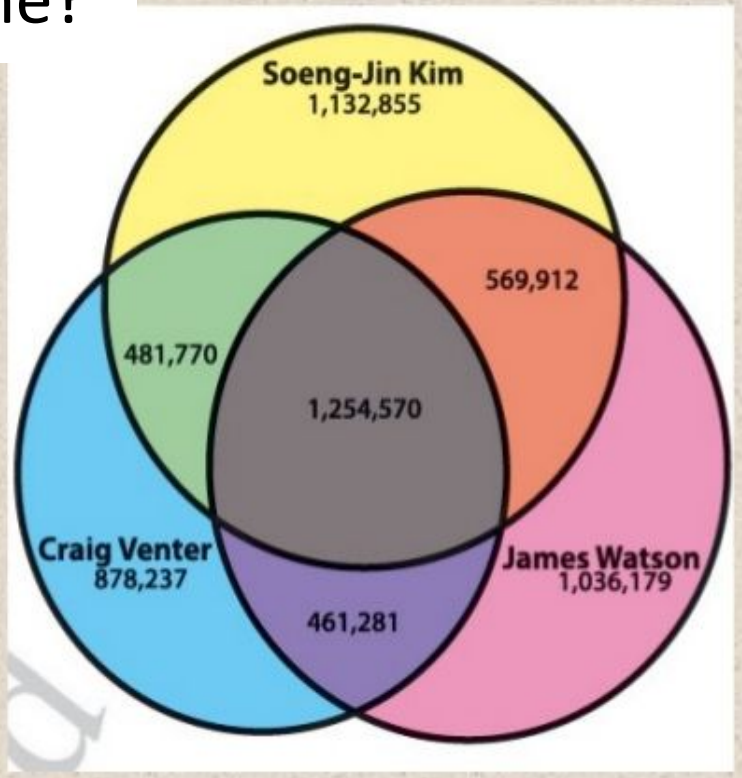


377 STR loci: Barbujani and Belle 2006

Un problema di scarsa risoluzione?

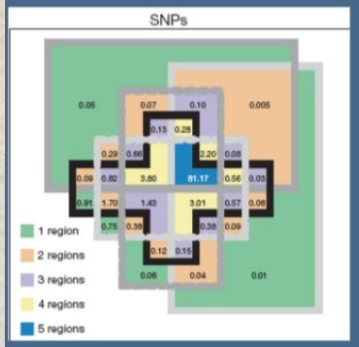
very large





At the genomic level, two people from the same country can be more different than people from different continents

Ahn et al. (2008) *Genome Res* **19:** 1622-1629

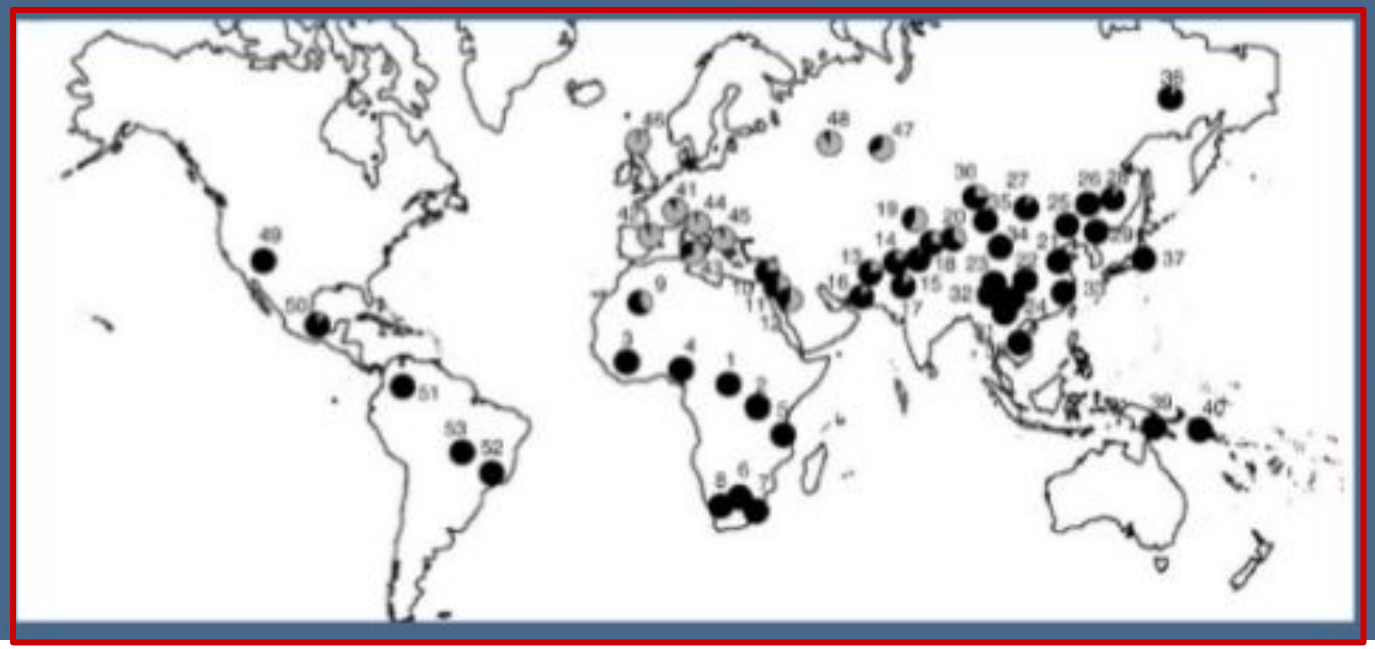


81% of SNPs cosmopolitan.

Alleles present in one continent only: 0.91% in Africa, 0.75% in Asia, practically 0 elsewhere.

Jakobsson et al. 2008
(525910 SNPs, 396 CNVs)

Genetic variation is discordant across loci



A meno che…

ASIP A8818G

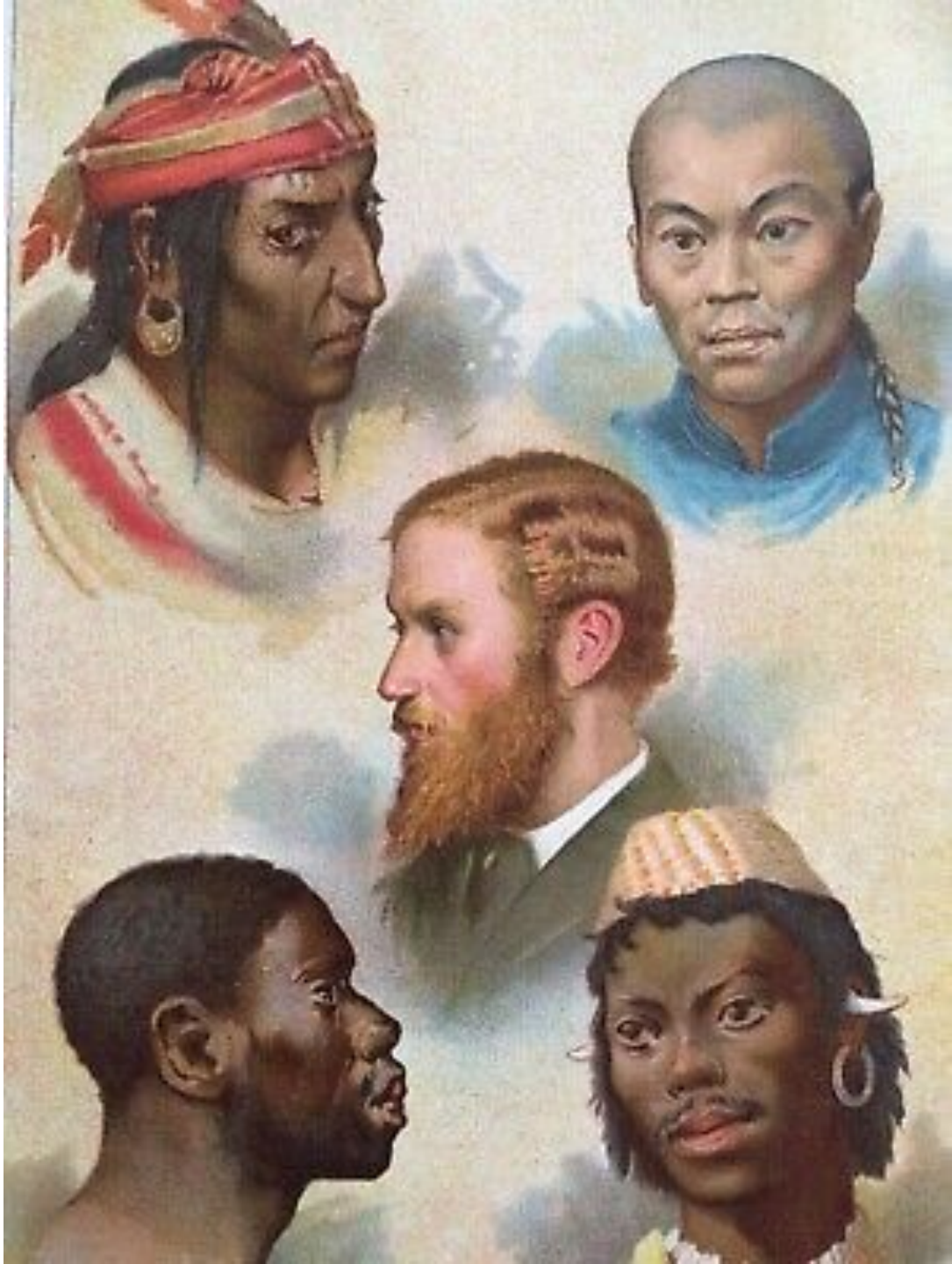
Agouti signaling protein, chromosome 20q11

mediates melanin synthesis. It may regulate the pH of the melanosome, affecting tyrosinase activity.[

SLC45A2

Membrane-assoc. transporter protein, chromosome 5

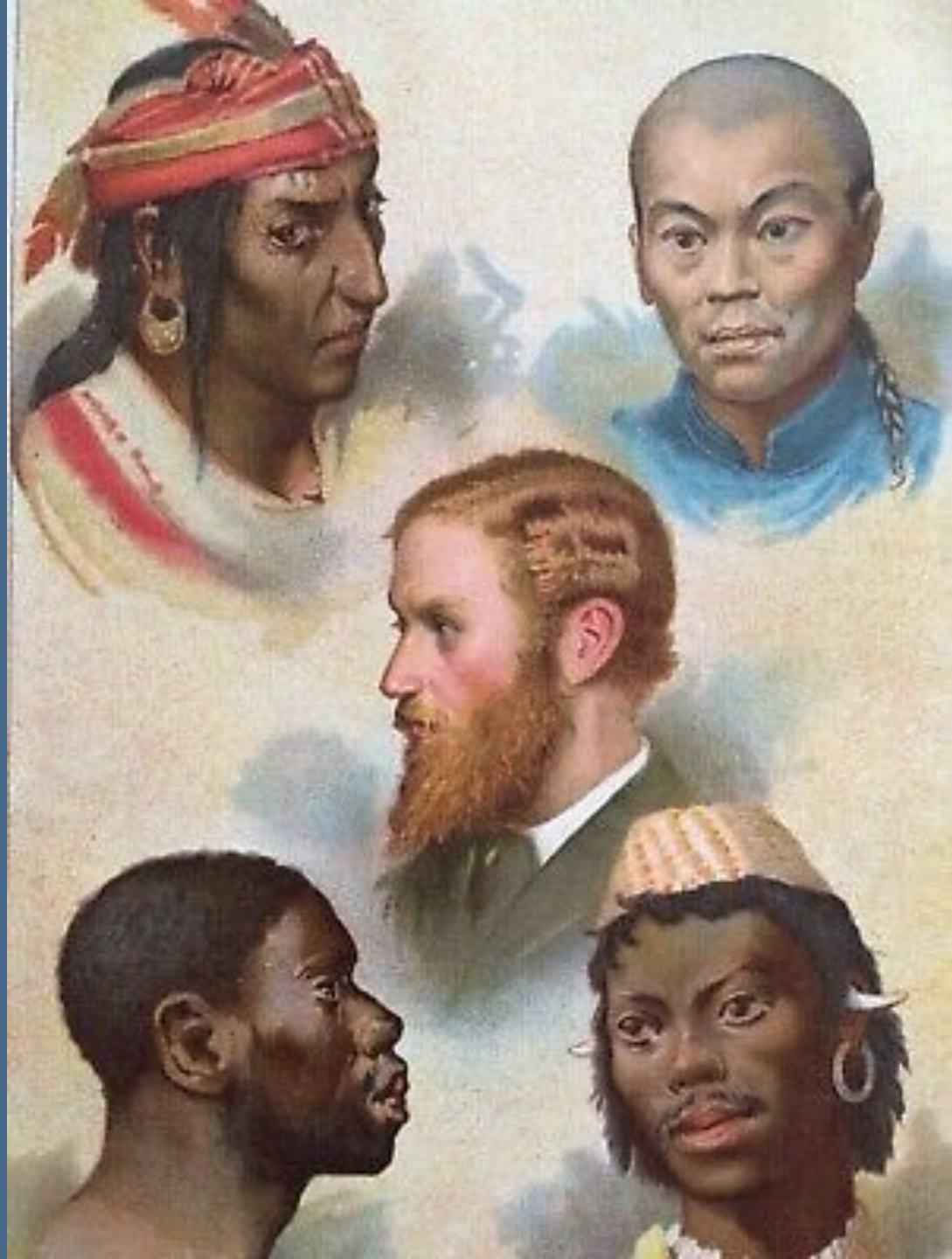
Ma perchè allora in passato (e anche oggi..) si è dato tanto credito al concetto di razza?



WARNING

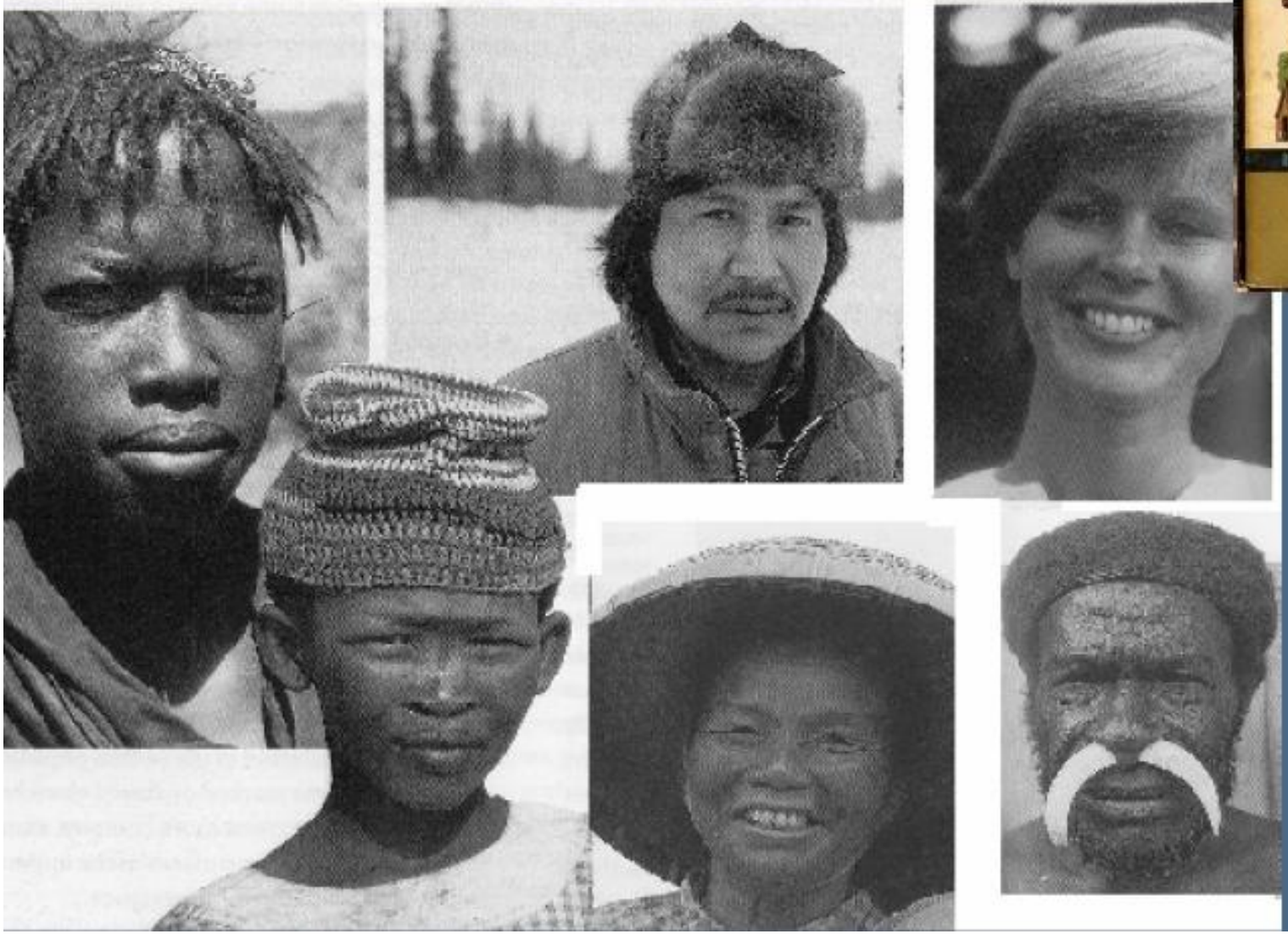
Sono il prodotto di più geni e dell'ambiente che può modificare la loro distribuzione (selezione naturale) ed espressione (statura).

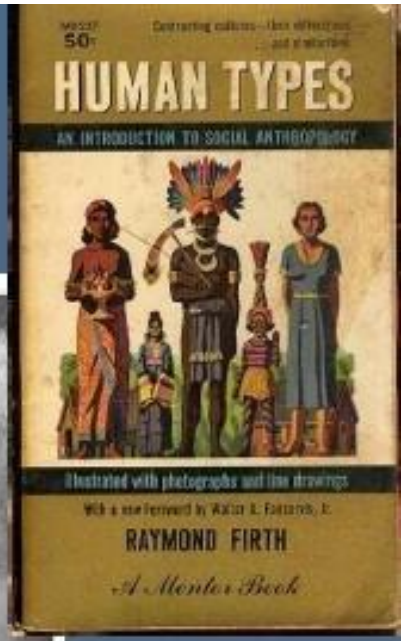
Quindi
Omoplasia?
Convergenza adattativa?



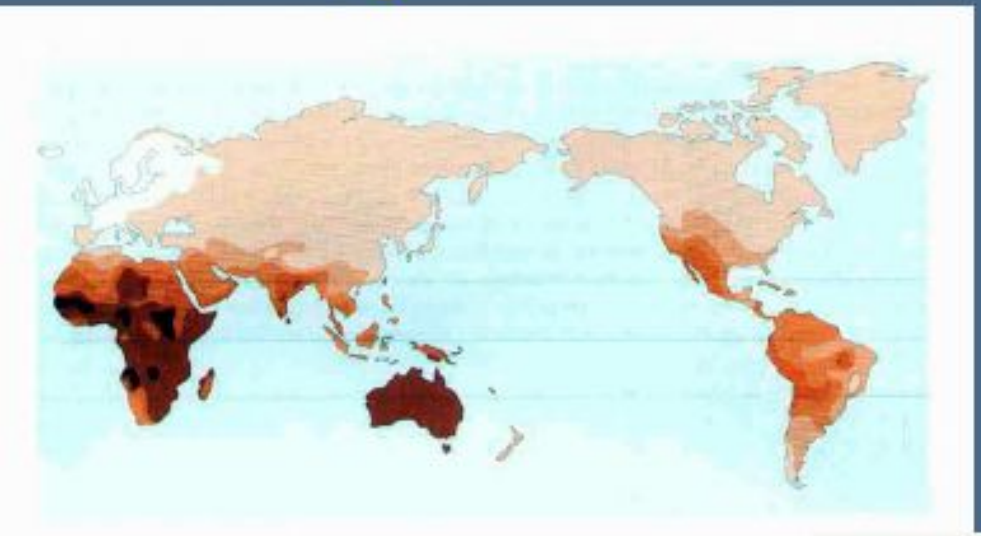
1. L’apparenza dei caratteri esterni inganna

Gruppi discreti?





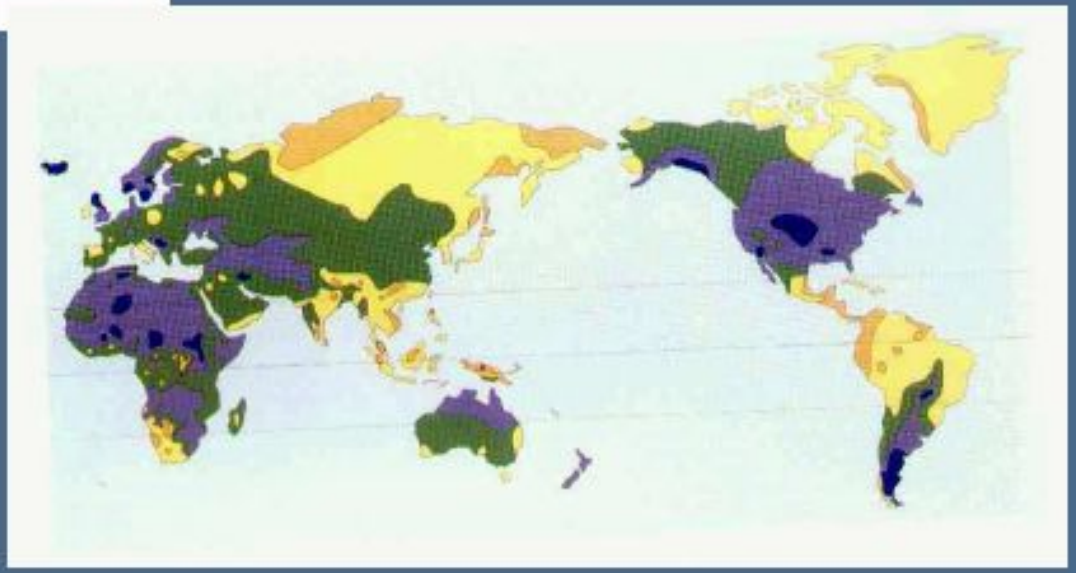
Il guaio dei caratteri morfologici



Gruppi discreti?

Colore della pelle

La variabilità è **continua** e **discordante**. Si possono classificare le persone sulla base di un carattere, ma altri caratteri porteranno a classificazioni differenti



Statura

Ma in ciascun gruppo ci sono molte differenze

Gruppi omogenei?

Lo studio della morfologia porta a cataloghi razziali contrastanti

Linneo (1735)	4 (europeus, luridus, afer, americanus) [+2]
Buffon (1749)	6 (europea, lappone, tartara, asiatica, etiopica, americana)
Blumenbach (1795)	5 (europeus, luridus, afer, americanus, australianus)
Cuvier (1828)	3 (caucasoide, negroide, mongoloide)
Huxley (1875)	4 (mongoloide, xantocroide, australoide, negroide)
Deniker (1900)	29
Weinert (1935)	17
Von Eickstedt (1937)	38
Museo di St. Nat., Chicago (1933)	107
Biasutti (1956)	56
Coon (1962)	5 (congoide, capoide, caucasoide, mongoloide, australoide)
Risch (2002)	5 (differenti in pagine differenti dello stesso articolo)

Proprio come con i polimorfismi genetici

Lo studio della morfologia porta a cataloghi razziali contrastanti

Linneo (1735)	4 (europeus, luridus, afer, americanus) [+2]
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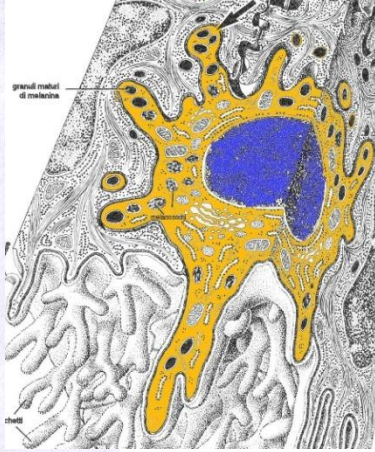
Biasutti (1956)	56
Coon (1962)	5 (congoide, capoide, caucasoide, mongoloide, australoide)
Risch (2002)	5 (differenti in pagine differenti dello stesso articolo)

2. IL colore della pelle (la percezione inganna)

Pigmentazione

Generalità



Pigmentazione cutanea, risultante di:

- melanina, pigmento scuro in granuli o diffuso, strato mucoso epidermide
  - emoglobina e pigmenti biliari
    - lipocromo, a base di carotene, nello strato corneo dell'epidermide

Melanociti

- Cellule di origine neuroectodermica, privi di nucleo e ricche di dendriti
- Strato basale dell'epidermide, bulbo pilifero e tratto uveale dell'occhio
- Originano dai melanoblasti (cresta neurale)

Variazioni della Pigmentazione con l'età e il sesso

- Si manifesta entro alcune ore dalla nascita, aumenta ne primi mesi
- Aumento della pigmentazione nella fase pre-puberale
- Maggiore pigmentazione del maschio, ma non nell'età puberale (fattori sociali)
- Diminuzione nel corso dell'età, + marcata nelle femmine

► Ereditabilità: 0.83 (f. interna braccio , 685 nm, Australiani, 1981)

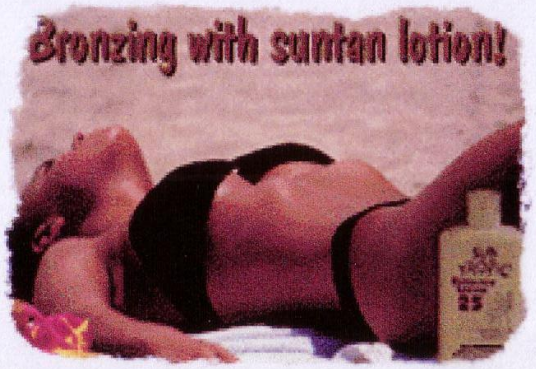
http://science.sciencemag.org/content/early/2017/10/11/science.aan8433

Pigmentazione

I pigmenti melaninici

- Eumelanina (bruno-nere)
- feomelanina (giallo brune)
- tricocromi (giallo rosso violetti)

sintesi dei pigmenti (nei melanosomi)



Nei melanociti, per effetto della luce:

$$\text{Tirosina} \xrightarrow{\text{tirosinasi} + O_2} \text{dopa} \xrightarrow{\text{dopaossidasi} + O_2} \text{dopachinone}$$

$$\text{dopacromo} \longrightarrow \text{indolo-5,6-chinone} \longrightarrow \text{omopolimero}$$

melanoproteina

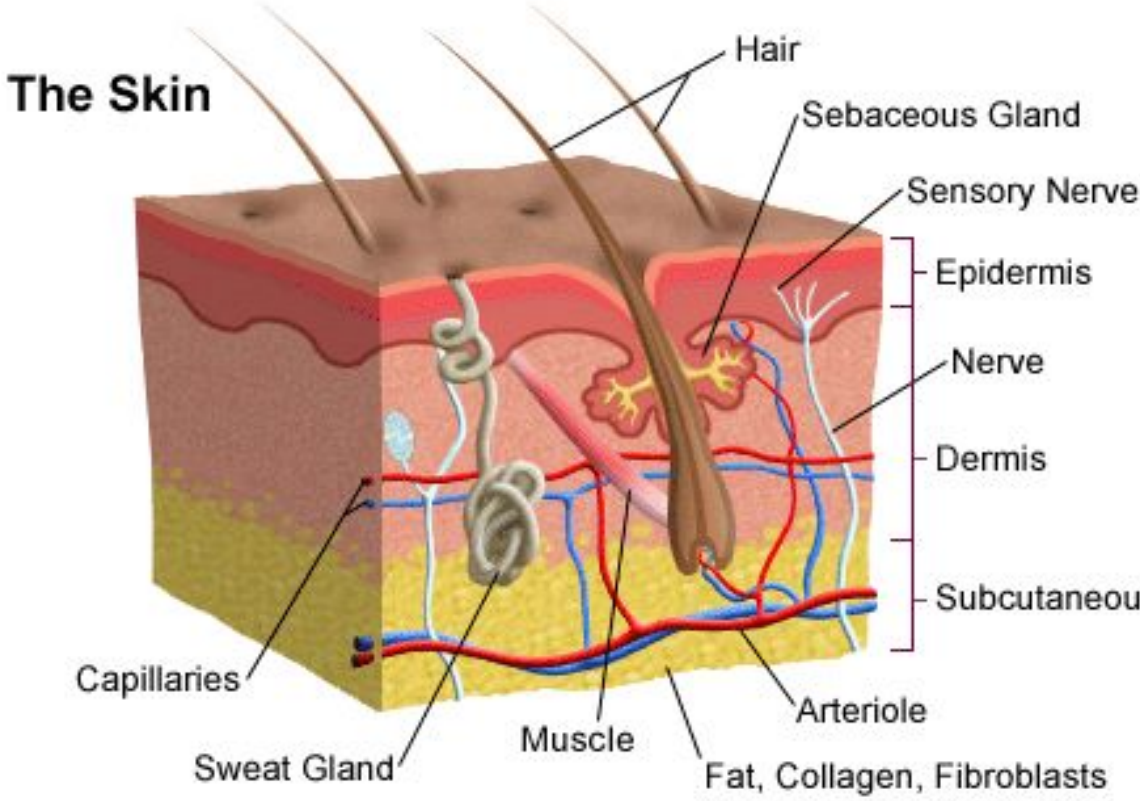
Cisteina o mercaptani

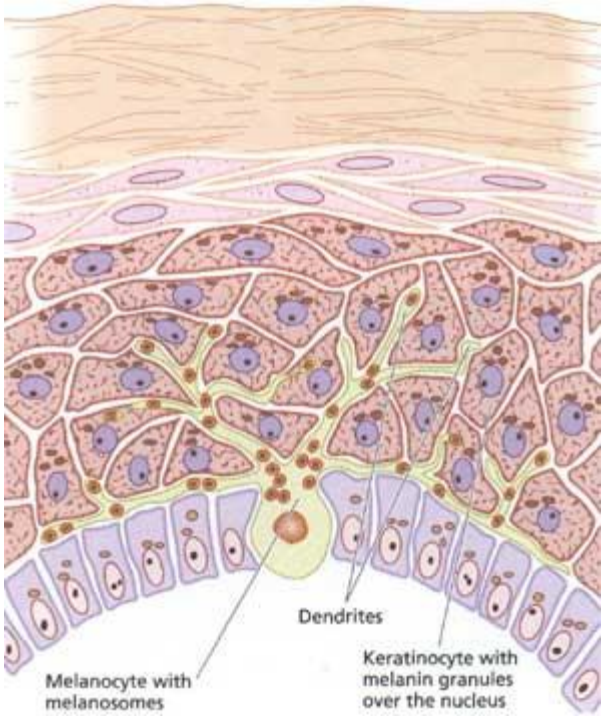
Feomelanine

tricocromi

Melanosomi ➡ dendriti del melanocita ➡ cheratinociti dell'epidermide ⬇

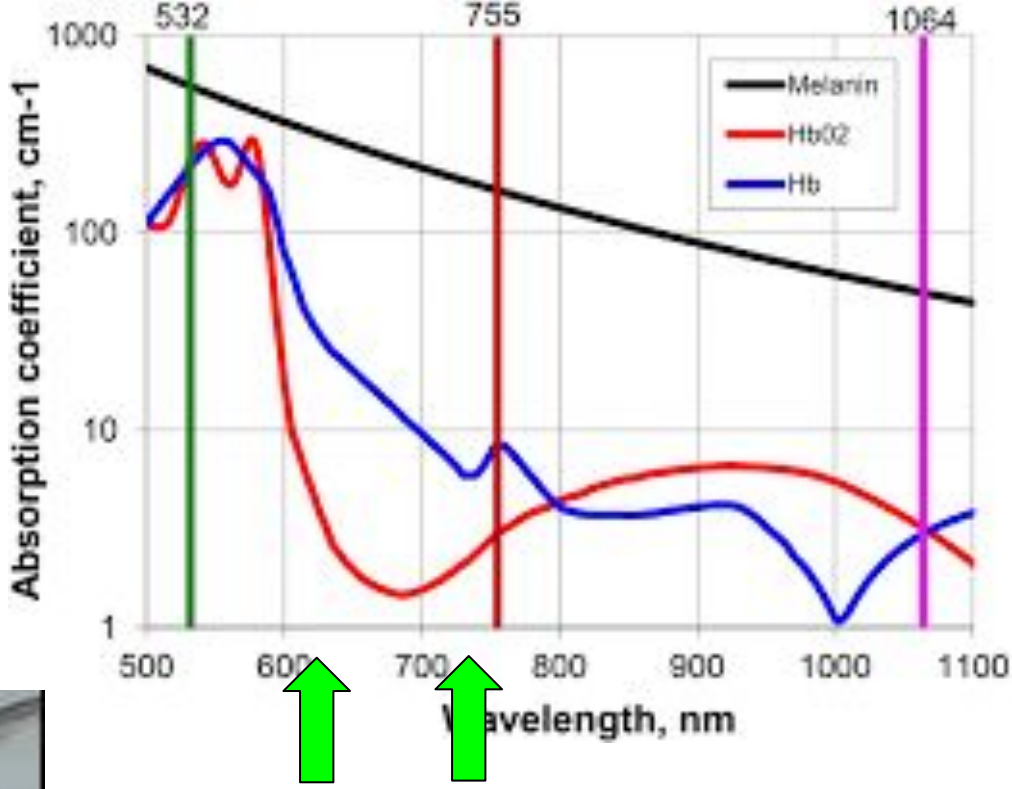
strati superficiali della pelle e bulbi piliferi

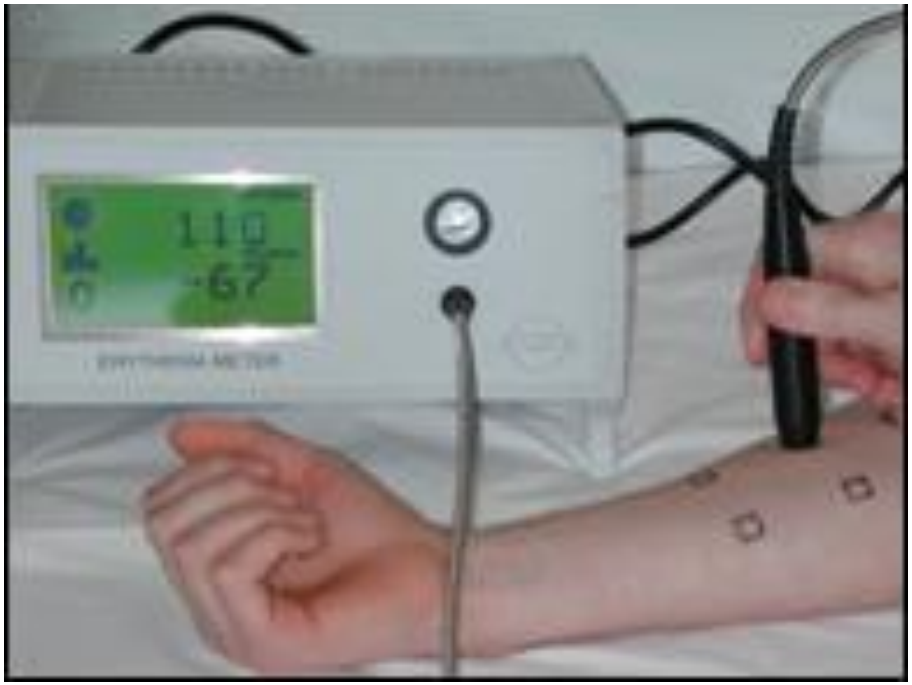




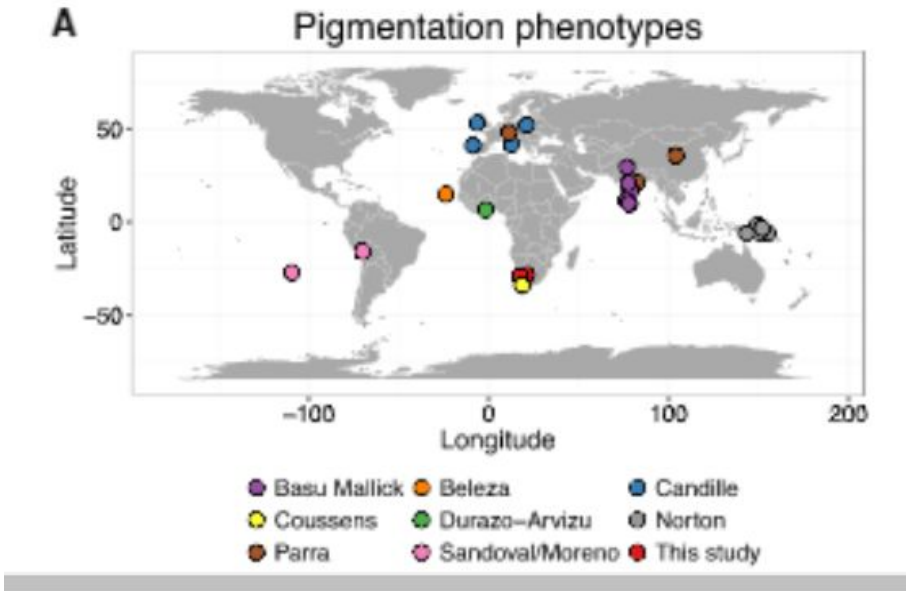
La melanina è contenuta all'interno dei **melanosomi** che possono essere presenti in uno spessore variabile dell'epidermide:

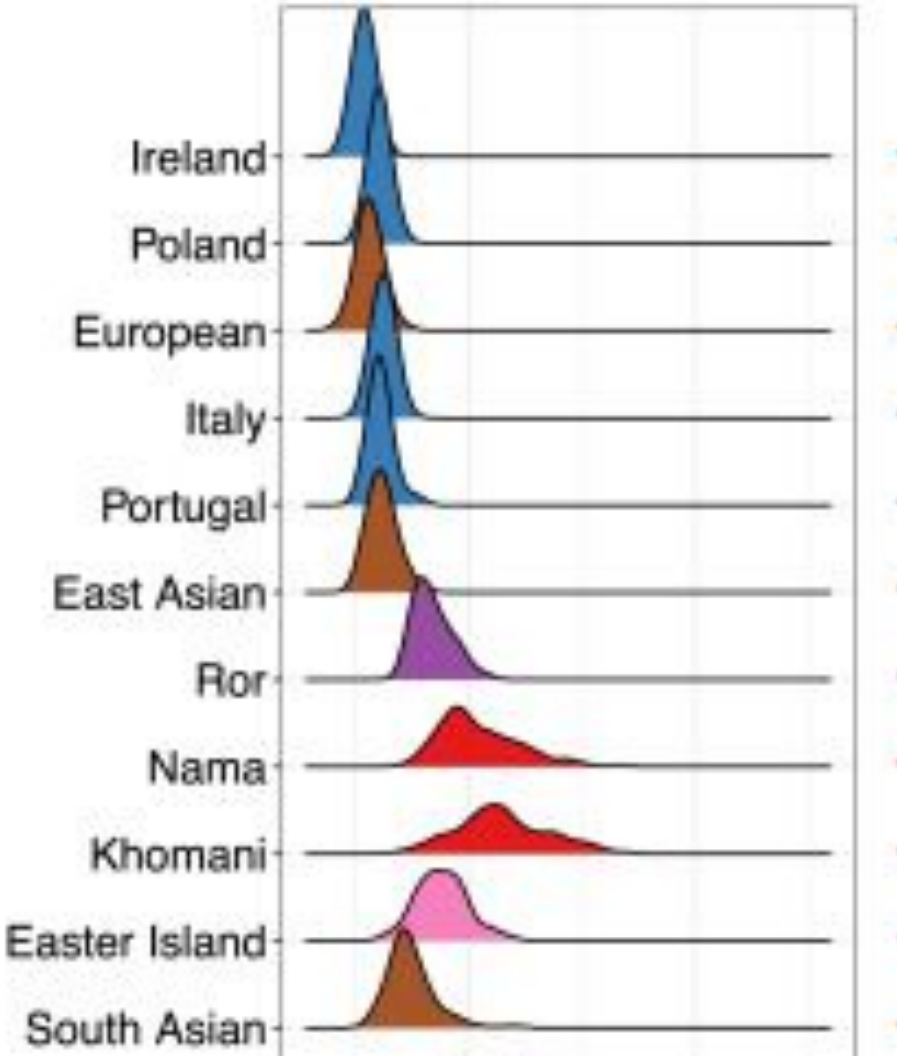
- **Epidermide germinativa**: strato più profondo dell'epidermide ed è sostenuto da una membrana basale che lo separa dal derma sottostante
- **Strato spinoso**
- **Strato granulare**





The melanin index (mx) is measured at 620- 720 nm nm

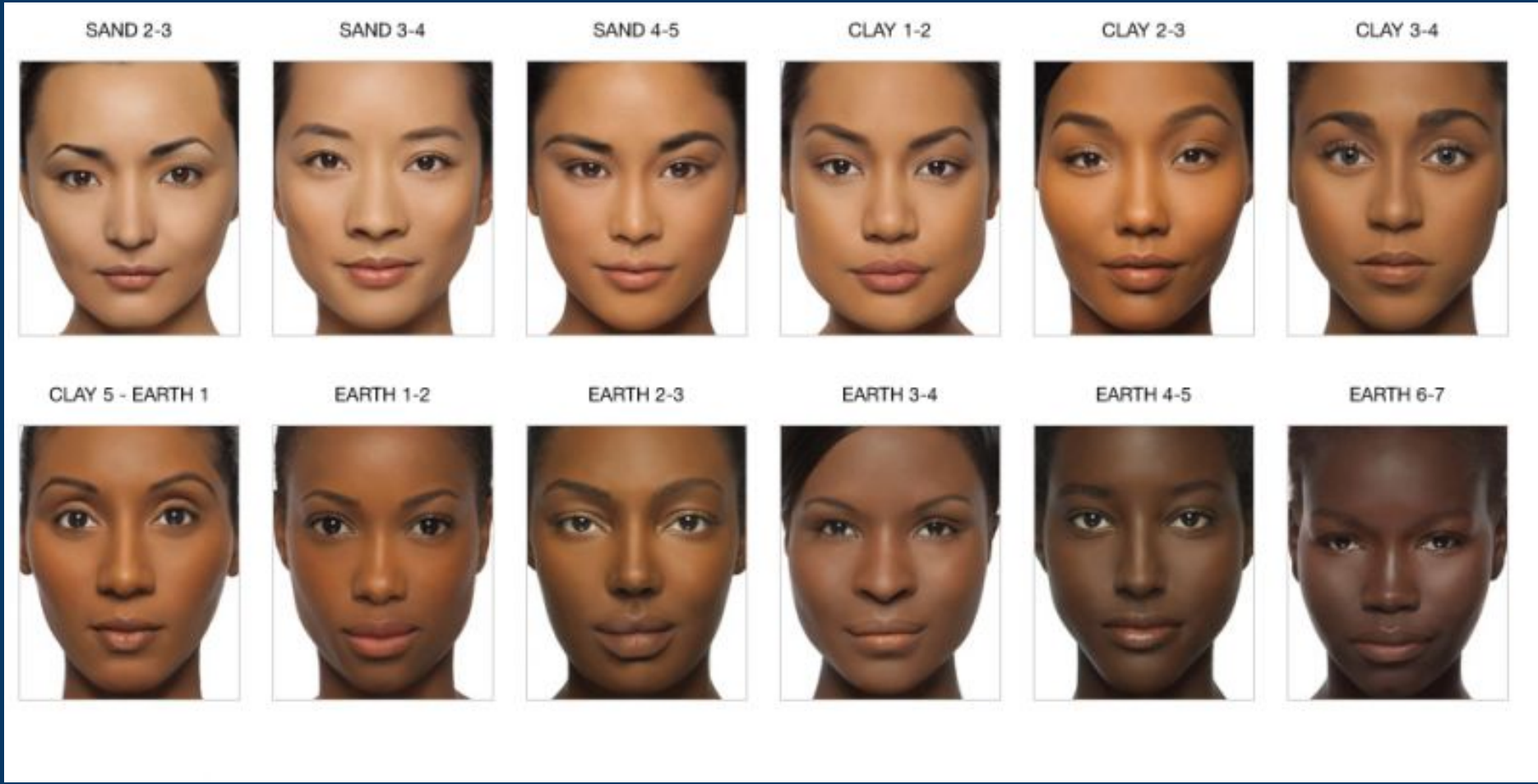




https://doi.org/10.1016/j.cell.2017.11.015

Violin plots of pigmentation distributions for 32 populations from 8 studies ordered by latitude; absolute latitudes provided on the right.

Bianchi, Neri e Gialli?
o piuttosto una variabilità continua?!



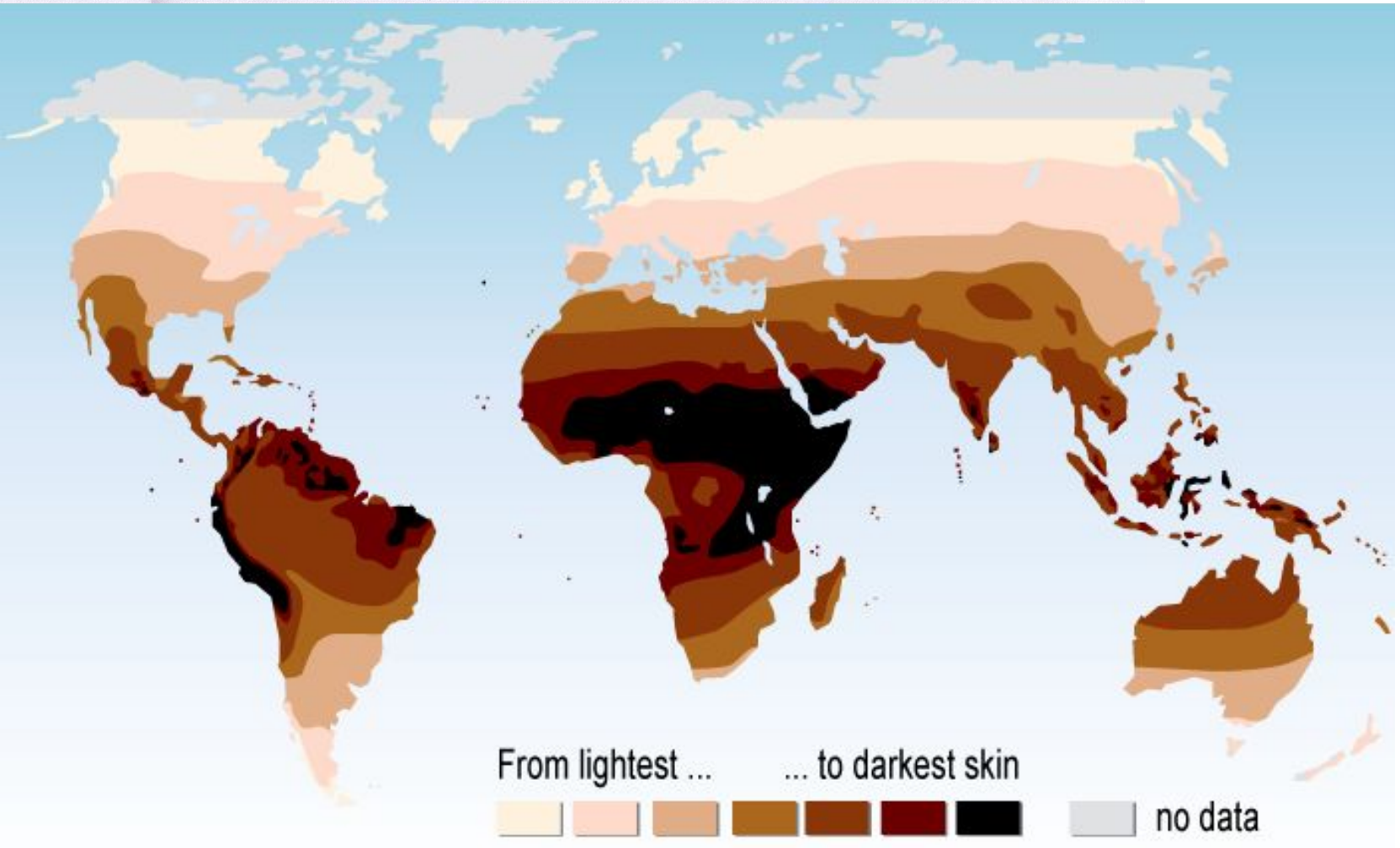
Pigmentazione distribuzione

Distribuzione della pigmentazione

- aumento dell'1% della riflettanza per ogni grado di distanza dall'equatore correlazione .82
- regola di Gloger
- > grado di pigmentazione nell'emisfero sud

Eccezioni

- Eschimesi
- Pigmei Africani
- Boscimani (p. giallastra)
- Paleoindidi
- Amerindiani



Cause della diversità del colore della pelle

sì Vitamina D e fissazione del calcio nelle ossa

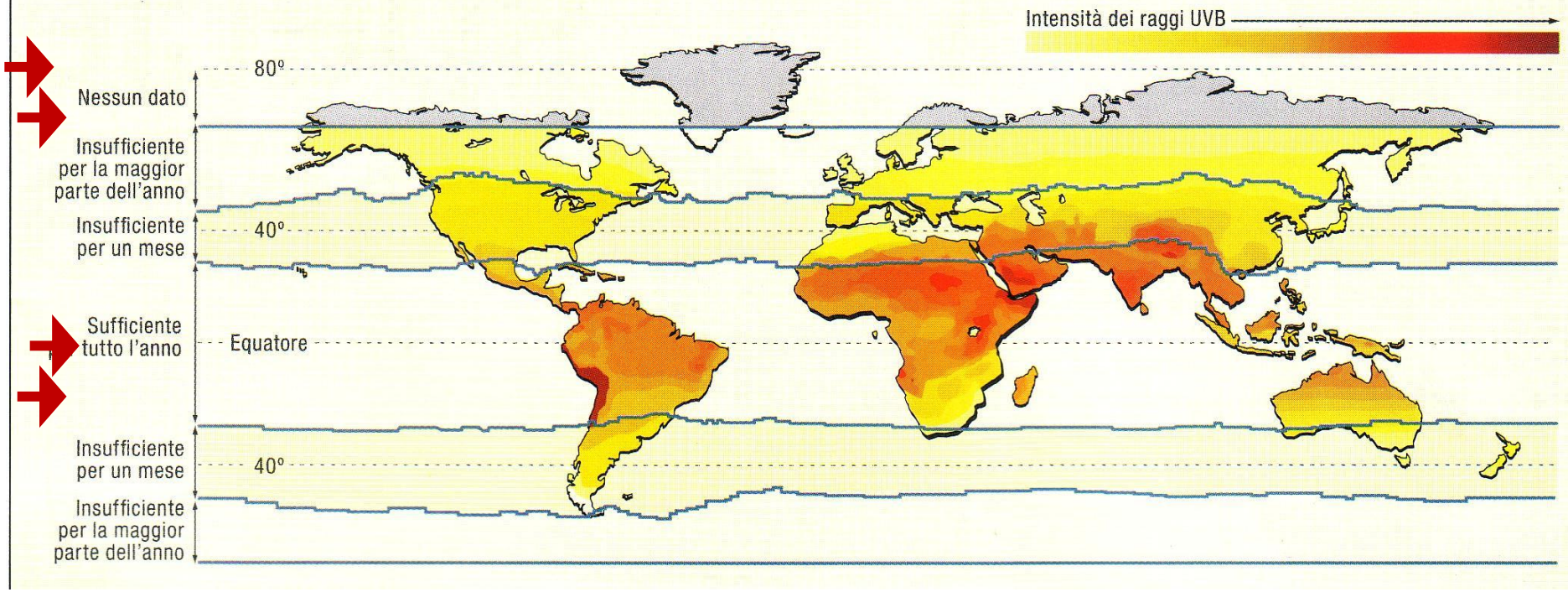
sì Acido folico

no Melanoma

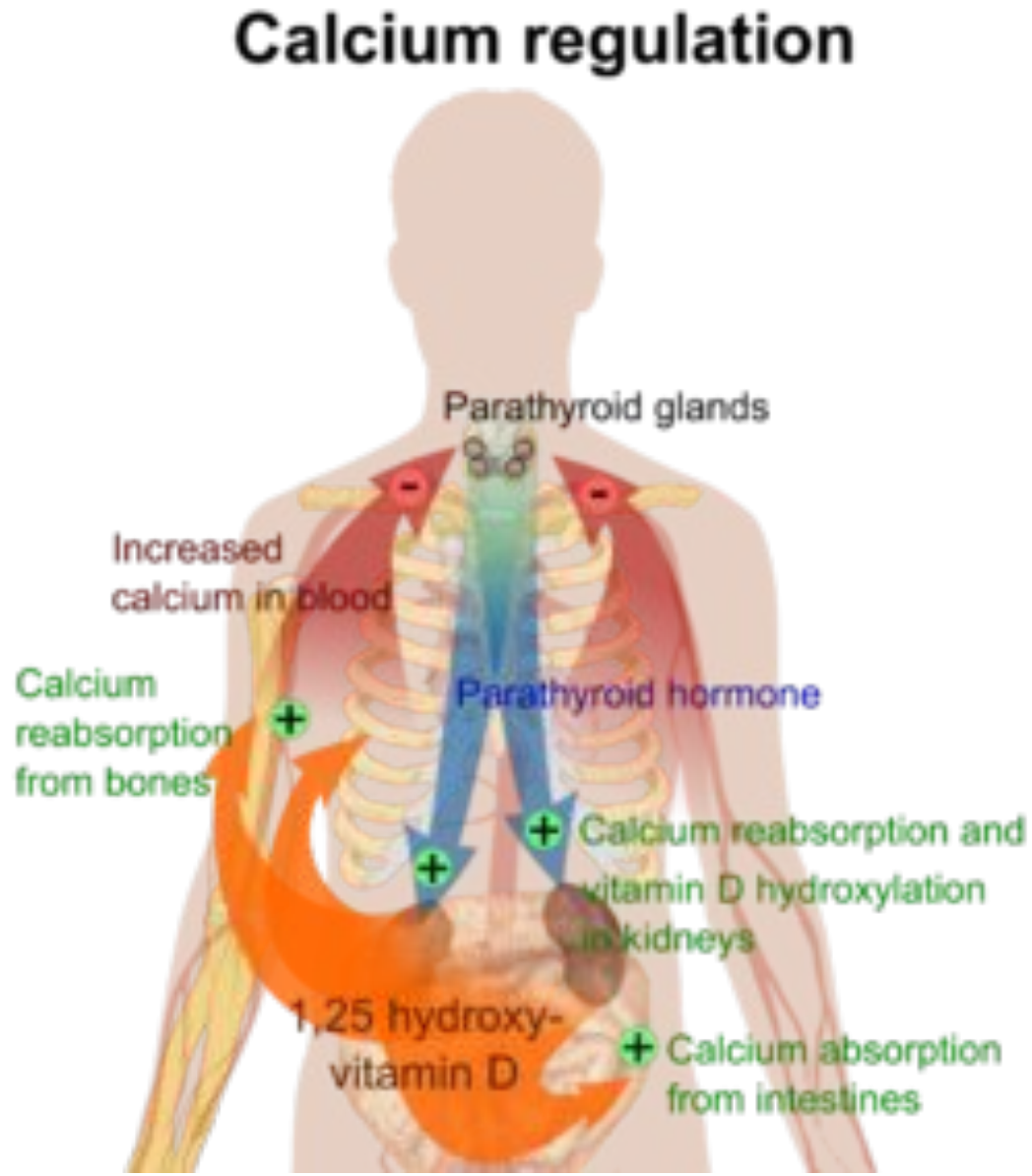
Cause della diversità del colore della pelle

L'inverno della vitamina D

Per la maggior parte degli individui l'esposizione ai raggi UVB provenienti dalla luce solare è la sola fonte principale di vitamina D, ecco perché regione e stagione incidono sul rischio di sviluppare ipovitaminosi. Per i periodi dell'anno noti come «inverno della vitamina D», a certe latitudini l'intensità dei raggi UVB è troppo debole anche solo per indurre la sintesi della vitamina D nella pelle. L'ozono blocca i raggi UVB, che quindi sono più intensi nei pressi dell'equatore, dove la luce del Sole percorre la distanza minima attraverso l'atmosfera terrestre e dove la sintesi della vitamina D è possibile durante tutto l'anno. Un angolo di incidenza maggiore, come quello corrispondente a latitudini più elevate, indebolisce l'intensità della radiazione UVB al punto da renderla insufficiente, specialmente d'inverno, per la produzione di vitamina D.



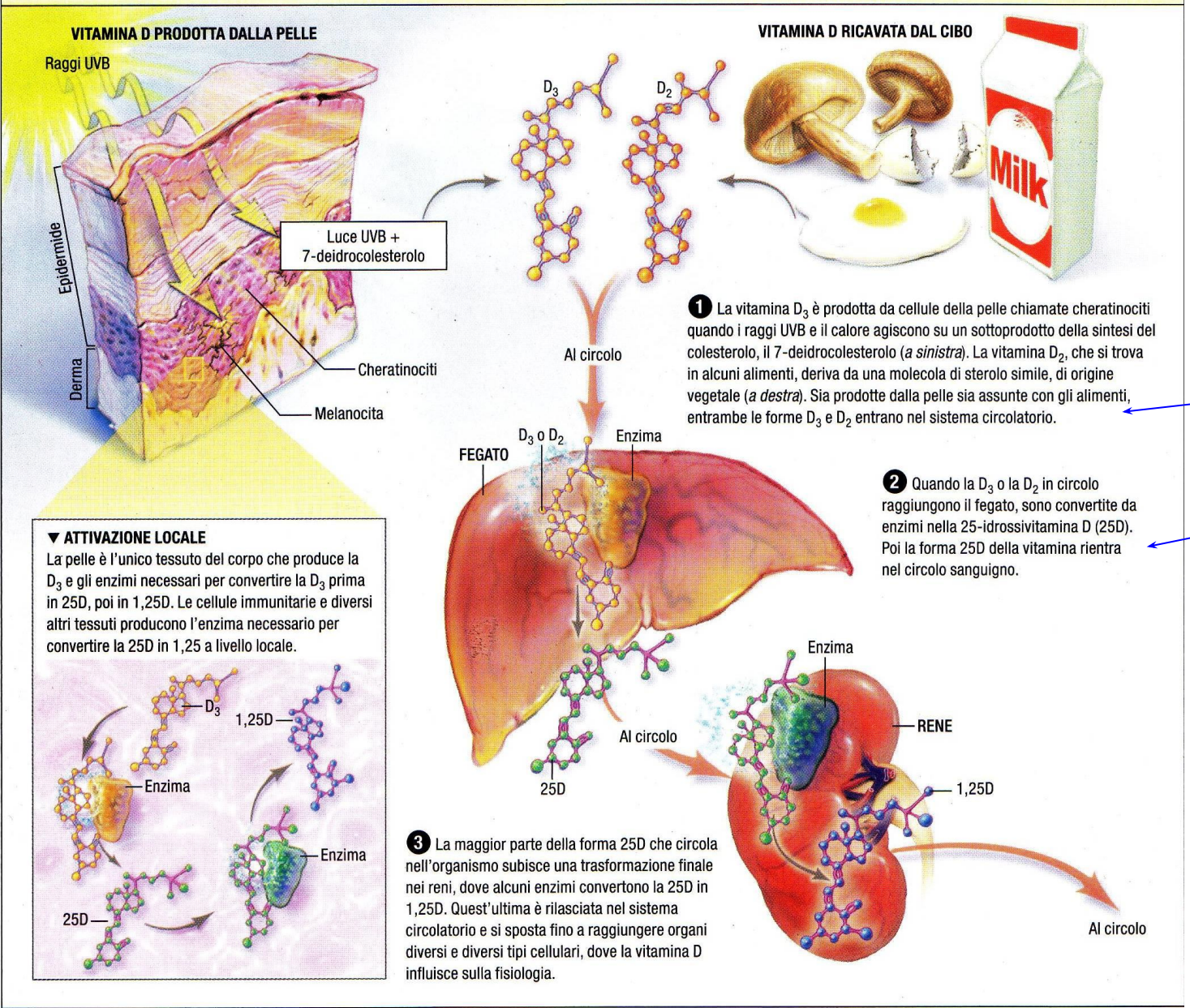
North or south of about 46°, levels of UVB are insufficient to initiate cutaneous production of previtamin D3 for much of the year



Cholesterol
ultraviolet
→
Previtamin D_3
isomerization
→
Vitamin D_3
Liver
→
Calcifediol
PTH + Kidneys
→
Calcitriol

Produzione di una vitamina attiva

Il termine «vitamina D» si riferisce a due molecole leggermente diverse tra loro: la cosiddetta D_3, prodotta dalla pelle umana, e la D_2, che è prodotta dalle piante e che le persone possono ottenere dal cibo. Tutte e due le versioni della vitamina D devono subire una conversione enzimatica per poi trasformarsi in una forma biologicamente attiva, nota con la sigla 1,25D.



❶ La vitamina D_3 è prodotta da cellule della pelle chiamate cheratinociti quando i raggi UVB e il calore agiscono su un sottoprodotto della sintesi del colesterolo, il 7-deidrocolesterolo (*a sinistra*). La vitamina D_2, che si trova in alcuni alimenti, deriva da una molecola di sterolo simile, di origine vegetale (*a destra*). Sia prodotte dalla pelle sia assunte con gli alimenti, entrambe le forme D_3 e D_2 entrano nel sistema circolatorio.

❷ Quando la D_3 o la D_2 in circolo raggiungono il fegato, sono convertite da enzimi nella 25-idrossivitamina D (25D). Poi la forma 25D della vitamina rientra nel circolo sanguigno.

❸ La maggior parte della forma 25D che circola nell'organismo subisce una trasformazione finale nei reni, dove alcuni enzimi convertono la 25D in 1,25D. Quest'ultima è rilasciata nel sistema circolatorio e si sposta fino a raggiungere organi diversi e diversi tipi cellulari, dove la vitamina D influisce sulla fisiologia.

D_3 e D_2

25D □ 1,25D

Ossa

Cervello

Cellule immunitarie

Fegato

Nervi

Pancreas

Prostata

cheratinociti

QUAL È LA CONCENTRAZIONE OTTIMALE?

Le stime sulle quantità di vitamina D disponibile per l'organismo si basano sulla concentrazione di 25D nel siero del sangue. Livelli fra 30 e 45 nanogrammi per millilitro di siero (ng/ml) sono considerati appena sufficienti per la salute delle ossa, anche se alcune risposte cellulari diventano ottimali a concentrazioni maggiori. Sotto i 30 ng/ml aumentano i rischi per la salute; sopra 150 si può verificare un eccessivo accumulo di calcio nei tessuti, e possono comparire sintomi di tossicità.

Sopra i 150 nanogrammi (ng)
Sintomi di tossicità e ipercalcemia

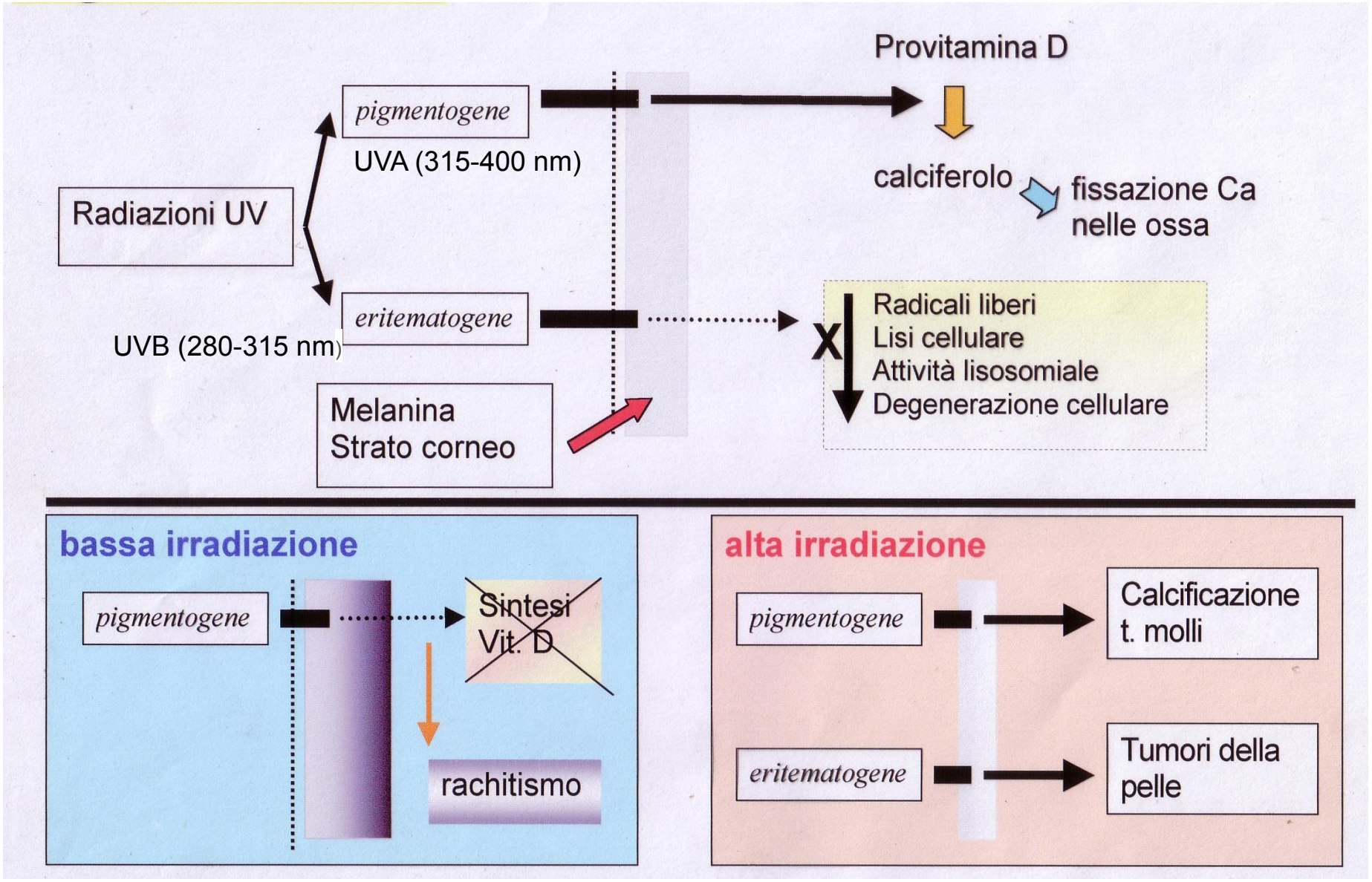
30-60 ng INTERVALLO PREFERIBILE

20-29 ng INSUFFICIENZA
L'assorbimento di calcio è inadeguato

0-19 ng CARENZA
Possono comparire sintomi di rachitismo
Aumenta il rischio di cancro
È inibita la risposta peptidica antimicrobica

Concentrazioni sieriche di 25D (ng/ml)

Vitamina D e selezione naturale



oltre la Vitamina D ...

Quindi: distribuzione della pelle come risultato della selezione contro rachitismo e ipercalcificazione

altri meccanismi alla base della distribuzione della pigmentazione?

Spettro	*Evento selettivo*	*Selezione per* pelle chiara	pelle scura
UV	ustioni da sole ?		X
	cancro della pelle		X
	ipervitaminosi D		X
	fotolisi alimentare		X
	deficienza di vitamina D	X	
visibile	difficoltà di essere visti		X
	acutezza visiva	X	
infrarosso	colpo di calore	X	
	congelamento	X *	
	malattie tropicali		X

pleiotropia

Acido folico

spina bifida e spermatogenesi

Human skin pigmentation as an adaptation to UV radiation

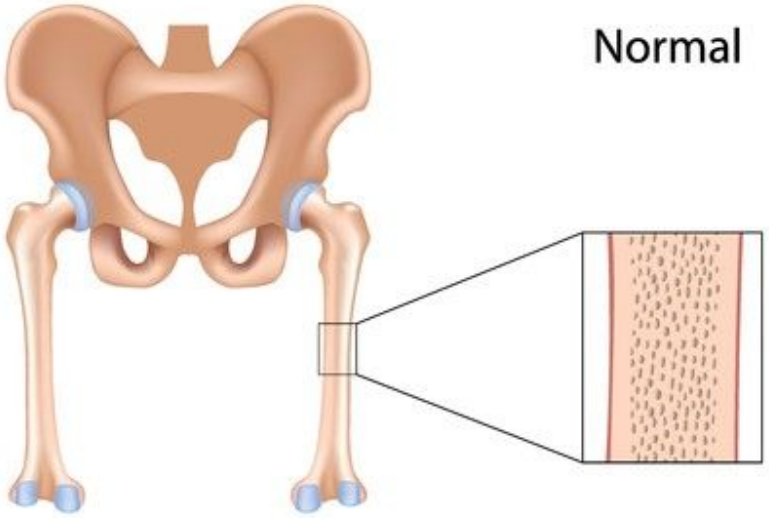
Nina G. Jablonski[1] and George Chaplin

Department of Anthropology, Pennsylvania State University, University Park, PA 16802

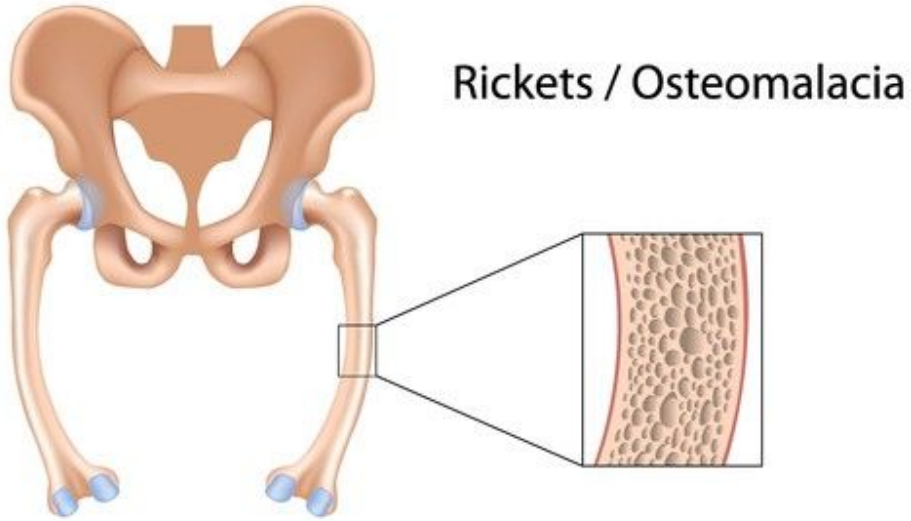
8962–8968 | PNAS | May 11, 2010 | vol. 107 | suppl. 2

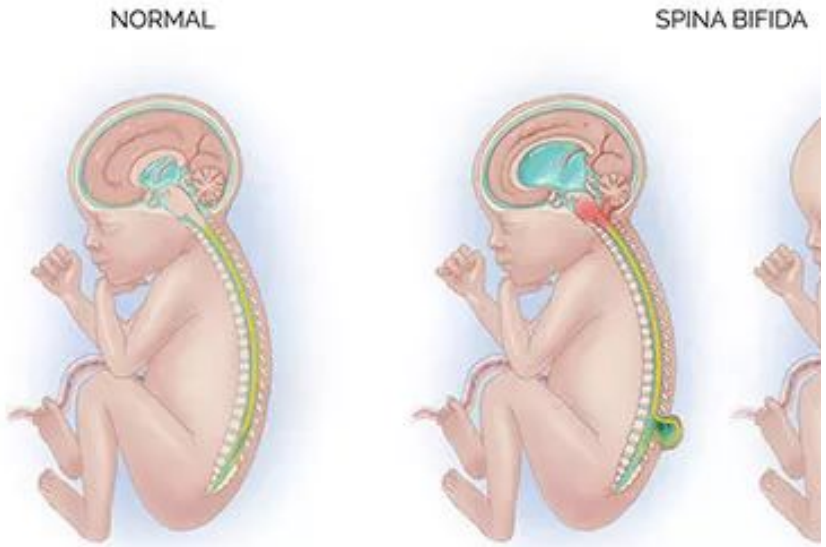
Table 1. Summary of the effects of UVA and UVB on human body and the selective mechanisms involved in the evolution of pigmentation. The estimated strength of natural selection operating to darken and lighten pigmentation is indicated by numbers of "+" and "–" signs, respectively. See text for references for proposed mechanisms.

Agent	Strength and direction of selection	Proposed selective mechanism(s)
UVA	+++	Photolysis of folate (as 5-methyltetrahydrofolate [5MTHF] in serum) directly and by ROS in the presence of flavins and porphyrins, resulting in reduction of folate available for cell division
UVA	++	Competition for folate: increased folate needs for DNA damage repair and as 1-carbon donor in methylation of DNA competing with folate needed for melanogenesis
UVA	++	Disruption of melanin production because of sensitivity of tyrosinase to high levels of ROS
UVA	+	Malignant melanoma (as the only skin cancer that causes death to individuals of reproductive age)
UVA	+	Photoconversion of excess vitamin D_3 to inactive metabolites
UVB	+++	Production of cyblobutane pyrimidine dimers and damaged nucleotides requiring repair resulting from DNA absorption of photons; activation of folate-dependent DNA repair processes
UVB	+	Direct photolysis of folate (as 5MTHF in serum), reducing the amount of folate available for cell division and regulation of tyrosinase activity in melanogenesis
UVB	+	Competition for folate: increased folate needs for DNA damage repair and as 1-carbon donor in methylation of DNA competing with folate needed for melanogenesis
UVB	No effect	Sunburn
UVB	No effect	Damage to DNA and its repair system and alterations of the immune system lead to progressive genetic alterations and the formation of nonmelanoma skin cancers
UVB	–	Cutaneous photosynthesis of vitamin D_3
UVB	–	Greater need for vitamin D in females probably causing increasing sexual dimorphism in pigmentation; exaggerated by sexual selection in some populations



Il **rachitismo** è una malattia tipica dell'età pediatrica ed è causato da un difetto di ossificazione del tessuto osseo di nuova formazione, soprattutto a livello delle cartilagini di coniugazione e delle zone di calcificazione provvisoria. Il rachitismo colpisce sia gli esseri umani sia gli animali nei primi mesi di vita.





La **spina bifida** è una malformazione o difetto neonatale dovuto alla chiusura incompleta di una o più vertebre, risultante in una malformazione del midollo spinale.

La complessità della genetica del colore della pelle

YEARBOOK OF PHYSICAL ANTHROPOLOGY ARTICLE

Shades of complexity: New perspectives on the evolution and genetic architecture of human skin

Ellen E. Quillen[1,2] | Heather L. Norton[3] | Esteban J. Parra[4] | Frida Lona-Durazo[4] | Khai C. Ang[5] | Florin Mircea Illiescu[6,7] | Laurel N. Pearson[8] | Mark D. Shriver[8] | Tina Lasisi[8] | Omer Gokcumen[9] | Izzy Starr[9] | Yen-Lung Lin[9] | Alicia R. Martin[10,11,12] | Nina G. Jablonski[8]

https://onlinelibrary.wiley.com/doi/epdf/10.1002/ajpa.23737

Like many highly variable human traits, **more than a dozen genes are known to contribute to the full range of skin color**. We are beginning to appreciate how limited our understanding of the genetic bases of human skin color have been. **Novel variants in genes not previously linked to pigmentation have been identified and evidence is mounting that there are hundreds more variants yet to be found.** Even for genes that have been exhaustively characterized in European populations like MC1R, OCA2, and SLC24A5, research in previously understudied groups is leading to a new appreciation of the degree to which **genetic diversity, epistatic interactions, pleiotropy, admixture, global and local adaptation, and cultural practices operate in population-specific ways to shape the genetic architecture of skin color.** Furthermore, we are coming to terms with how factors like tanning response and barrier function may also have influenced selection on skin throughout human history. By examining how our knowledge of pigmentation genetics has shifted in the last decade, we can better appreciate how far we have come in understanding human diversity and **the still long road ahead for understanding many complex human traits**.

evoluzione convergente!

TABLE 1 Summary of skin color genetics association studies discussed in this manuscript

Study	Study type[a]	Trait	N	Continent	Population	N[b]	Associated genes
Abe, Tamiya, Nakamura, Hozumi, & Suzuki, 2013	Candidate gene (4)	Melanin Index	456	Asia	Japanese	1	*OCA2*
Ang et al., 2012	Candidate gene (2)	Melanin Index	492	Asia	Peninsular Malaysia	2	*SLC24A5, SLC45A2*
Beleza, Johnson, et al., 2013	Admixture mapping	Melanin Index	699	Africa	Cape Verdean	4	*SLC24A5, TYR, OCA2, SLC45A2*
Candille et al., 2012	GWAS	Melanin Index	469	Europe	Ireland (146), Poland (72), Italy (109), Portugal (142)	0	
Crawford et al., 2017	GWAS	Melanin Index	1,570	Africa	Ethiopia, Tanzania, Botswana	6	*SLC24A5, MFSD12, DDB1, TMEM138, OCA2, HERC2*
Eaton et al., 2015	Candidate gene (9)	Melanin Index	419	Asia	East Asian Ancestry (Canada)	1	*OCA2*
Han et al., 2008	GWAS	Melanin Index	10,755	Europe	European Ancestry (U.S. and Australia)	3	*SLC24A4, IRF4, SLC45A2*
Hernandez-Pacheco et al., 2017	GWAS	Melanin Index	658	Americas	Hispanic/Latinos from Puerto Rico (285) and African Americans (373)	4	*SLC24A5, SLC45A2, BEND7, PRPF18*
Jonnalagadda, Norton, Ozarkar, Kulkarni, & Ashma, 2016	Candidate gene (5)	Melanin Index	533	India	Western India	1	*SLC24A5*
Liu et al., 2015	GWAS	Self-Report	17,262	Europe	Dutch (5,857), Australian (4,296), UK (5,278)	5	*SLC45A2, IRF4, HERC2/OCA2, MC1R, ASIP*
Marcheco-Teruel et al., 2014	Candidate gene (15)	Melanin Index	1,019	Americas	Cuba	2	*SLC24A5, SLC45A2*
Martin, Lin, et al., 2017	GWAS	Melanin Index	456	Africa	KhoeSan	4	*SLC24A5, TYRP1, SMARCA2/VLDLR, SNX13*
Nan et al., 2009	GWAS	Tanning response	15,155	Europe	European Ancestry (U.S.)	5	*SLC45A2, IRF4, TYR, OCA2, MC1r*
Norton et al., 2007	Candidate gene (6)	Melanin Index		Asia	Island Melanesia	2	*OCA2, ASIP*
Norton, Werren, & Friedlaender, 2015	Candidate gene (9)	Melanin Index	583	Americas	European Ancestry (U.S. and Canada)	3	*SLC45A2, IRF4, HERC2*
Paik et al., 2011	Linkage analysis	Melanin Index	345	Asia	Mongolia	4	*GRM6, ATF1, WNT1, SILV/Pmel17*
Quillen et al., 2011	Candidate (14)	Melanin Index	515	Americas	Mexico (95), U.S. Hispanics (247), Colombian (173)	4	*SLC24A5, SLC45A2, OPRM1, EGFR*
Rawofi et al., 2017	GWAS	Melanin Index	305	Asia	East Asian Ancestry (Canada) & Chinese	1	*ZNF804B*
Shriver et al., 2003	Admixture Mapping Candidate (3)	Melanin Index	592	African/European	African American (232), European American (187), and African Caribbean (173 U.K.)	2	*TYR, OCA2*

(Continues)

MC1R

Diversity

melanocyte-stimulating hormone receptor (**MSHR**)

- key protein involved in regulating mammalian skin and hair color: a large protein family of transmembrane receptors that sense molecules outside the cell and activate inside signal transduction pathways and, ultimately, cellular responses.

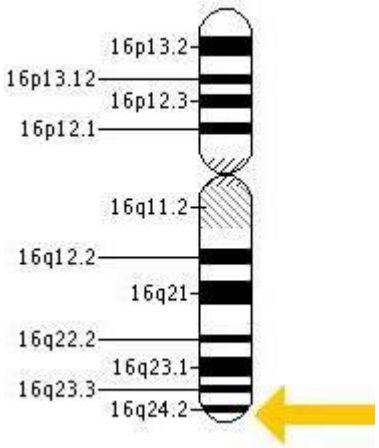
- G protein-coupled receptor which binds to a class of pituitary peptide hormones (melanocortins, e.g. melanocyte-stimulating hormones)

- from (red) pheomelanin to (black, photoprotective) eumelanin.

- pheomelanin: UV-induced skin damage by free radicals upon UV radiation

MC1R

melanocyte-stimulating hormone receptor (**MSHR**)
melanin-activating peptide receptor



long (q) arm of chromosome 16 at position 24.3

intronless gene

size < 1 KB

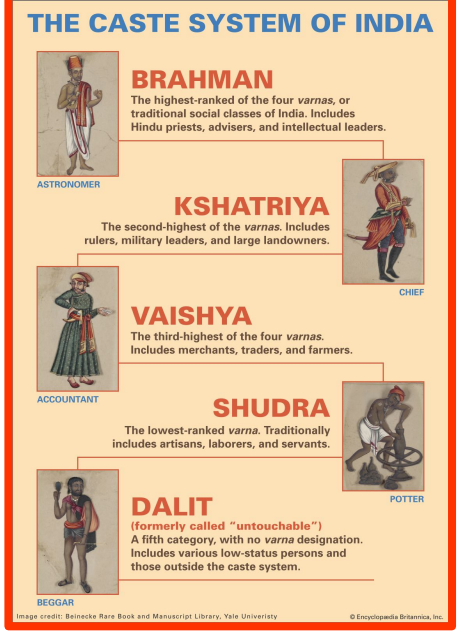
65 alleles

highly polymorphic in Northern European populations
not in Africa: selection against light skin

Loss of function mutations
- increased pheomelanin production
- freckling, skin color and beard color
- predisposition to skin cancer

SLC24A5

Epistasis the effect of a gene mutation is dependent on the presence or absence of mutations in one or more other genes, respectively termed **modifier genes**.



solute carrier family 24 member 5

also known as **Sodium/potassium/calcium exchanger 5** (NCKX5)

a member of the potassium-dependent sodium/calcium exchanger family.

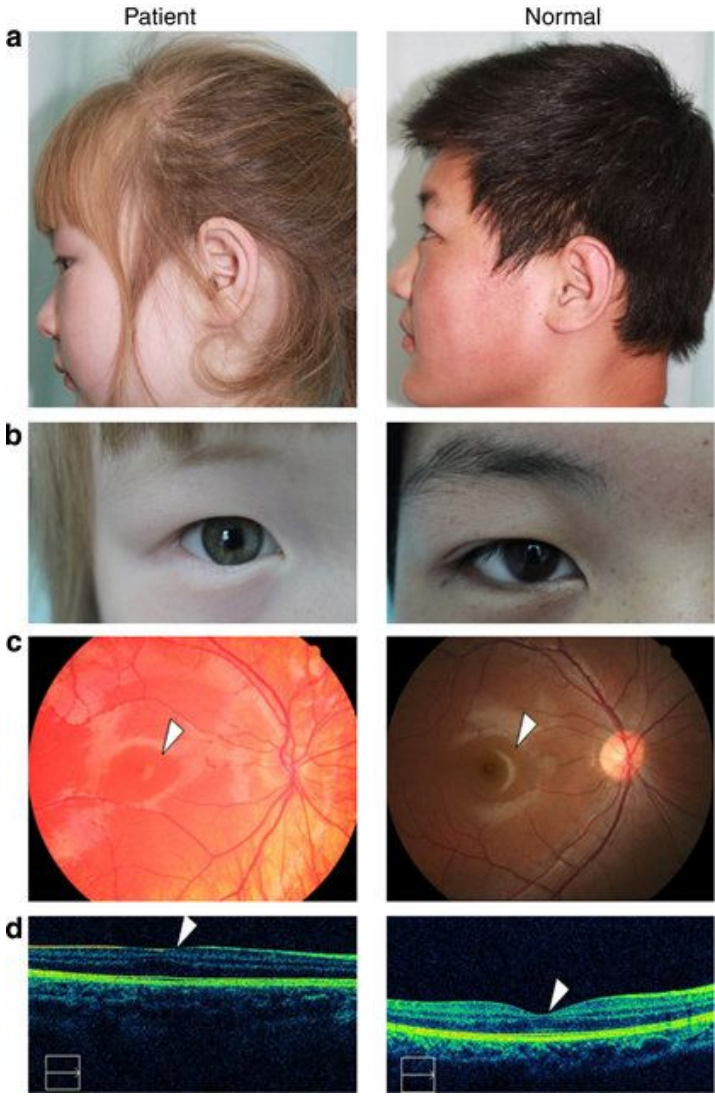
SNP rs1426654
polymorphism with the G and A alleles of the encoding alanine or threonine, respectively, at amino acid 111 in the third exon

The impact of Ala111Thr on skin color, however, varies across the Indian subcontinent depending on the epistatic context; the SLC24A5 111Thr allele's ability to lower melanin production is dependent on specific and distinct genetic backgrounds made possible by the unique reproductive structure (caste marriage) of the Indian populations (Iliescu et al., 2018).

Pleiotropy

Oculocutaneous albinism II (OCA2)

- located on the long (q) arm of chromosome 15
- encodes for **melanocyte-specific transporter protein,** an integral membrane protein involved in small molecule transport, specifically of tyrosine - a precursor of melanin.
- Mutations in OCA2 may result in type 2 oculocutaneous albinism.
- OCA2 east Asian variant clearly impacts skin, iris, and hair color i; seems to be the main determinant of eye color depending on the amount of melanin production in the iris stroma



La storia dei geni del colore della pelle

Crawford et al., Science 2017

Is it true that as humans migrated **out of Africa,** it was believed that mutations led to lighter skin that can supposedly regulate vitamin D production in lower sunlight levels?

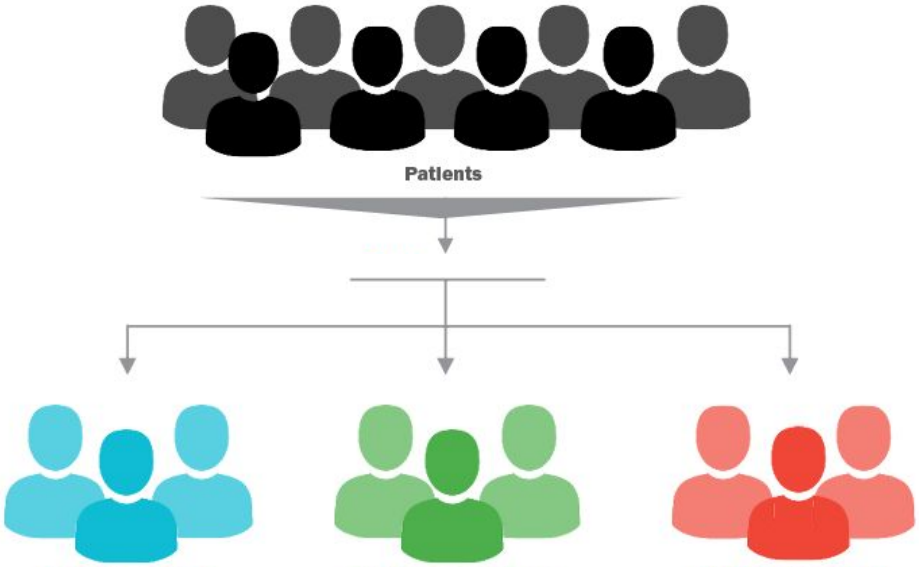
The genes for light skin have been there since the beginning. Chimp has light pigmentation, so skin color in the ancestors of modern humans could have been relatively light. It is likely that **when we lost the hair covering our bodies and moved from forests to the open savannah, we needed darker skin.**

Seven genetic variants associated with lighter skin developed at least 270,000 years ago and four more than 900,000 years ago. Considering our species, Homo sapiens, did not evolve until around 200,00 to 300,000 years ago, **genes responsible for lighter skin tones were present into the genetic material of our hominin ancestors—hundreds of thousands of years before the first humans walked the Earth.**

3.

Ciò che può sembrare utile non è per forza vero.

Race-based Pharmacogenetics?



Race	**Europe**	**Africa**	**Asia**
Treatment	**A**	**B**	**C**

Race-based medicine ?

YES, if

- Races have the potential to be biologically meaningful.
- Race-based medicine helps create genome-based personalized medicine

NO, since

- The concept of race in humans has no biological basis
- Difference in disease prevalence between two socially defined groups does not necessarily imply genetic causation
- Medical practices should maintain their focus on the individual rather than an individual's membership to any group
- Overemphasizing genetic contributions to health disparities carries various risks such as reinforcing stereotypes, promoting racism or ignoring the contribution of non-genetic factors to health disparities
- Epidemiological data show that living conditions rather than race make the biggest difference in health outcomes
- Patients are reluctant to accept racial categorization in medical practice.

VIEWPOINT

Race and Pharmacogenomics—Personalized Medicine or Misguided Practice?

Christopher W. Goodman, MD
Department of Medicine, University of South Carolina School of Medicine, Columbia.

Allan S. Brett, MD
Department of Medicine, University of South Carolina School of Medicine, Columbia.

Viewpoint pages 623 and 627

The use of race in clinical decision-making is coming under increasing scrutiny, in part because of growing recognition that race-based diagnosis and treatment reflect flawed social, biological, and genetic assumptions. Despite this concern, guidelines, algorithms, and advisory and regulatory bodies (including the US Food and Drug Administration [FDA]) regularly use race in ways that influence clinical decisions. For example, race-based "corrections" have been deemed problematic in algorithms, risk scores, and physiologic calculations used in cardiology, nephrology, urology, and obstetrics.[1,2]

Pharmacogenomics is a field that explores relationships between genes and drug effects, with potential to "personalize" medical therapy. For clinical scenarios in which a genotype is clearly linked to important outcomes, direct genetic testing would appear to obviate people of Southeast Asian and African American descent should be tested for the HLA-B*5801 allele before initiation of allopurinol.[4]

However, genetic variation within certain geographic populations or ethnic groups can exceed variation across racial categories. Published HLA-B*5801 allele frequencies demonstrate this intrapopulation genetic diversity and the limitations of the ACR recommendations (Figure). Data from Switzerland—available by city, not by race or ethnicity—illustrate the point. Despite Switzerland's relatively small size and comparative racial homogeneity, HLA-B*5801 frequencies vary considerably across the country. Although the average HLA-B*5801 frequency in Switzerland is comparable with the US White population, the city of Basel reportedly has a higher frequency of HLA-B*5801 than the US African American population.[5]

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isosorbide dinitrate/hydralazine HCl

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I am a healthcare provider interested in prescribing BiDil to my patients

I am a patient/ caregiver interested in learning about BiDil for African Americans with heart failure

isosorbide dinitrate	hydralazine HCl
releases nitric oxide	may also mitigate tolerance to nitrates
dilates arteries and veins	dilates arteries

1. the original study did not have **a significant number of African-American subjects** to make the BiDil's race specific claims,[] and that the results of **only one clinical trial** where African-Americans were tested does not provide a full and comprehensive study.

2. **Self-identified racial identifications** from patients as an indicator for race during the trials were not a sufficient categorization method because these self-identifications were socially constructed and have no biological connection to genomic data-

3. **the trial failed to include any non-African American test subjects**.[22] The trial was designed to include only African American test subjects, therefore failing to show that BiDil has a greater effectiveness in African Americans than those in other races.

4. **The trials represented a new form of scientific racism** where race, a socially constructed category, would continue to be present in research as a placeholder for genomic identification.

Another story

Yancy *et al.* (2001), a drug called **carvedilol**, which blocks the function of beta-adrenergic receptors, a type of hormone receptor in the body, **worked equally well** as a treatment for both African American and Caucasian patients with heart failure.

Exner *et al.*, 2001, another drug called **enapril**, which blocks the action of a protein known as angiotensin-converting enzyme (**ACE)**, was shown to be more effective in Caucasian patients with a particular heart defect than in African Americans. As a result of this study, there was a reported decrease in the offering of ACE inhibitors to treat hypertension in African American patients.

Saunders & Gavin (2007) have shown that when **adequate dosing and appropriate combinations are used**, ACE inhibitor therapy provides effective blood pressure control in both groups of patients ().

in **2008, Liggett *et al.***, found a mutation in G-protein-coupled receptor kinase 5 (GRK5) in 40% of African Americans. This mutation protects individuals suffering from heart failure from death and thus has an effect similar to beta-blocker drugs following heart failure. The authors concluded that this finding suggests "a reason for conflicting results of beta-blocker clinical trials in this population."

Am. J. Hum. Genet. 76:268–275, 2005

Genetic Structure, Self-Identified Race/Ethnicity, and Confounding in Case-Control Association Studies

Tang *et al.* (2005)
326 microsatellites in 3,636 people who identified themselves as belonging to Caucasian, African American, East Asian, and Hispanic).

Analysis of the data produced four major genetic clusters, which showed near-perfect correspondence with the four self-reported race/ethnicity categories.

Tang and colleagues thus concluded that using self-identified race as a way to divide populations in clinical studies is valuable, because that definition encompasses genetic variations.

Population genetic structure of variable drug response

James F. Wilson[1,2], Michael E. Weale[3,4], Alice C. Smith[1], Fiona Gratrix[1], Benjamin Fletcher[3], Mark G. Thomas[3], Neil Bradman[3] & David B. Goldstein[1]

Published online: 29 October 2001, DOI: 10.1038/ng761

Because different populations have different frequencies of various alleles involved in drug metabolism, Wilson *et al*. examined variations in genes encoding these enzymes, including CYP2D6, across the clusters they identified with their microsatellite analysis. They found that the genetic groupings (based on the microsatellite analysis) appeared to be more informative regarding differences in drug metabolism than the groupings based on skin color or self-defined ethnic groups.

Population	A	B	C	D
Bantu	0.04	0.02	0.93	0.02
Ashkenazi	0.96	0.01	0.01	0.02
Ethiopia	0.62	0.08	0.24	0.06
Norway	0.96	0.02	0.01	0.01
Armenia	0.90	0.04	0.02	0.05
China	0.09	0.05	0.01	0.84
Papua New Guinea	0.02	0.95	0.01	0.02
Afro-Caribbean	0.21	0.03	0.73	0.03

Table 1: Proportion of membership of each sampled population in structure-defined subclusters

These results indicate that a reasonably high number of loci should be used to obtain consistency in clustering; one approach would be to use one marker from each chromosome arm.

…ci and drug
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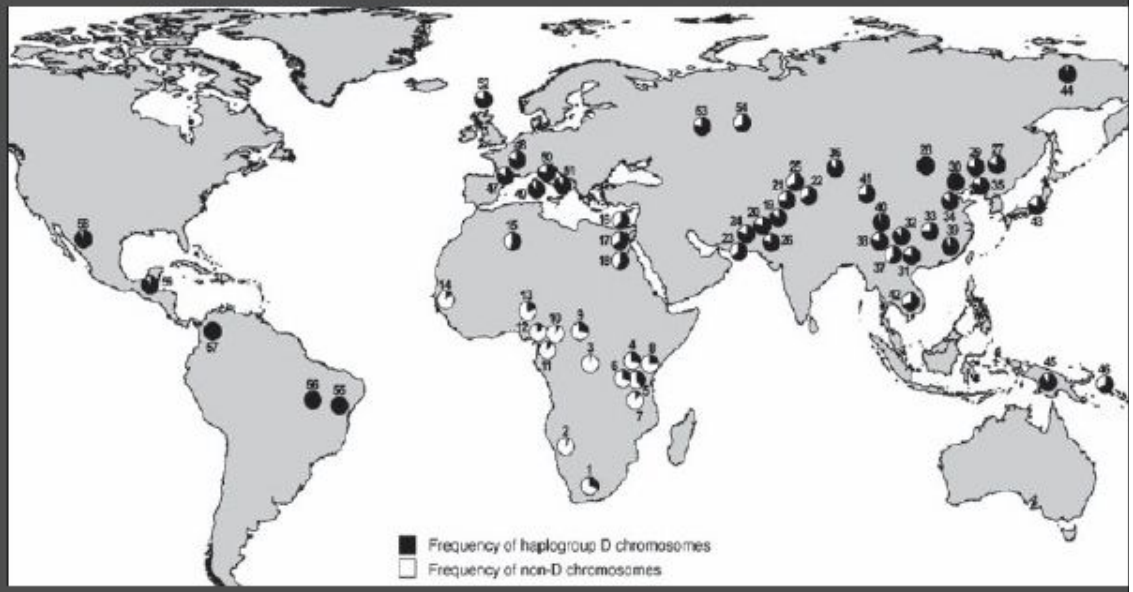
- 16 microsatellites on chromosome 1 and 23 on the X chromosome in a heterogeneous group of individuals. Study participants were then assigned to four subclusters according to their microsatellite alleles, which roughly corresponded to four geographic areas: Western Eurasia, Sub-Saharan Africa, China, and New Guinea (Table 1).

The trouble with genetic traits

NAT2 acetylator

MCPH D-haplogroup

Variation is **continuous** and **discordant**. It is possible to cluster people one the basis of any trait, but the resulting classification does not allow one to predict clustering for other traits



Race-based medicine ?

YES

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NO

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Symptoms based approach

Diagnosis → Disease X → *Treatment Decision* → Treatment A → *Treatment Fails* → Treatment B

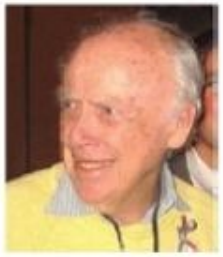
Stratified medicine approach

Genetic and bespoke diagnostic tests → *Stratification into disease subcategories*

Treatment Decision → Treatment B

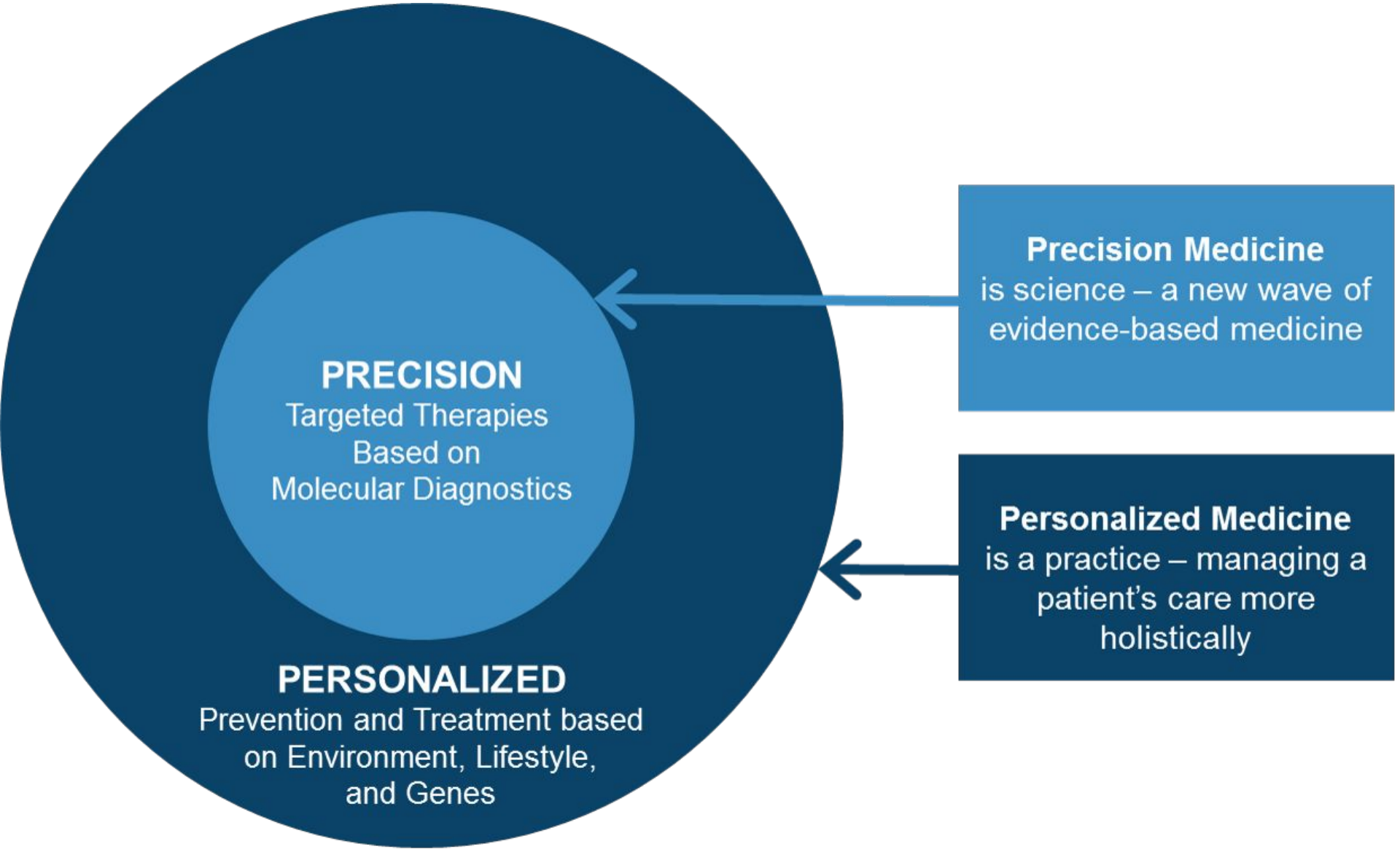
Treatment Decision → Treatment C

"To attain truly personalized medicine, the scientific community must leave behind simplistic race-based approaches, and look instead for the genetic and environmental factors contributing to individual drug reactions"

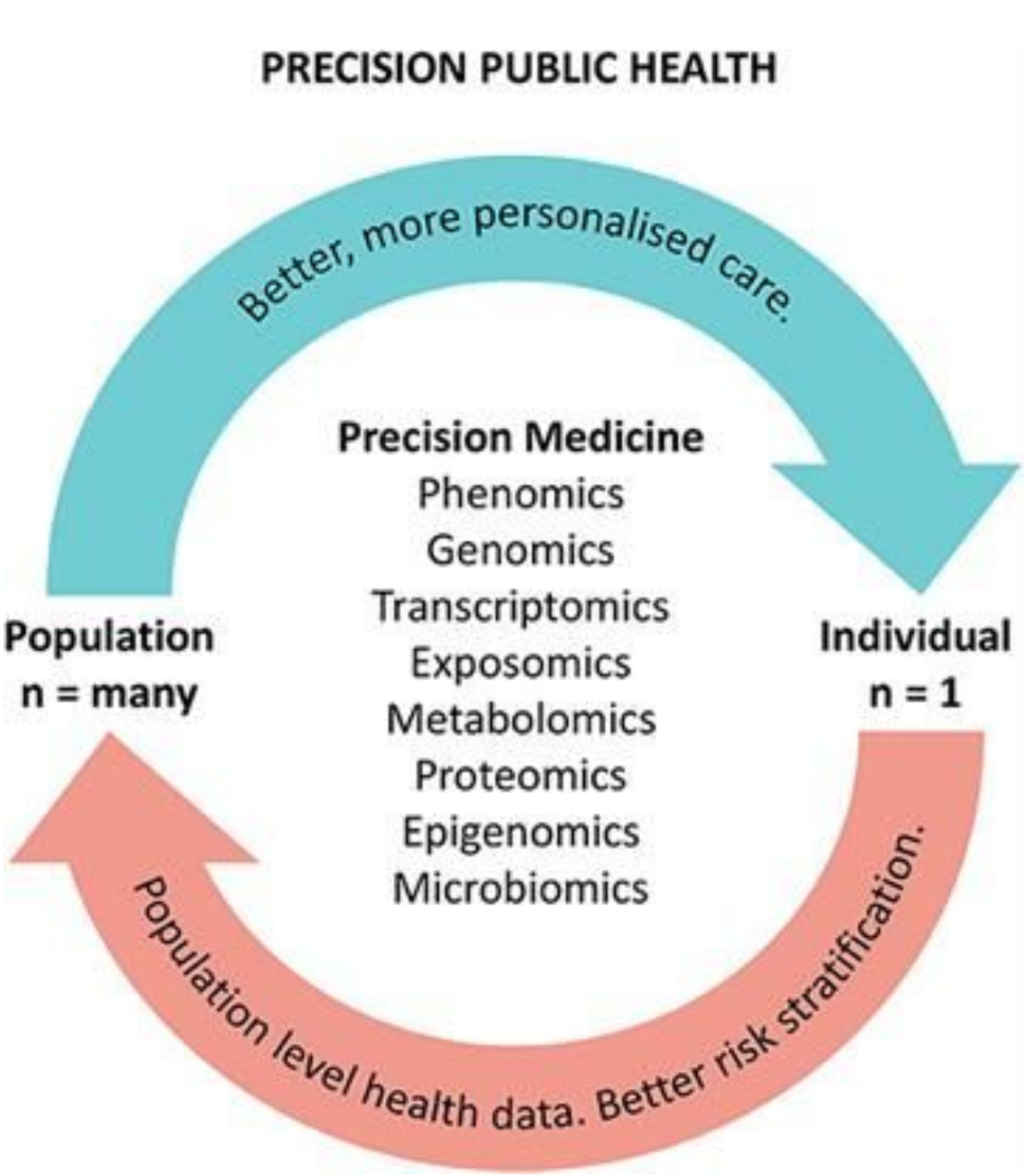


Gene	Examples of substrates	James Watson	Craig Venter	Known effects
CYP1A2	Antipsychotics, caffeine, warfarin	**1F/*1F*	**1F/*1F*	**1F* influences the induction of *CYP1A2* activity
CYP2C9	Anti-inflammatory drugs, statins, warfarin, sulfonylurea (antidiabetic), angiotensin receptor blockers (hypertension)	**1A/*1A*	**1A/*1B*	**1B* appears to be normal
CYP2C19	Proton pump inhibitors, tricyclic antidepressants	**1B/*1B*	**1B/*1B*	**1B* has normal enzyme activity
CYP2D6	β-Blockers, antiarrhythmics, antipsychotics, tricyclic antidepressants	**10/*10*	**1A/*1A*	**10* has decreased activity
CYP3A4	Calcium channel blockers, chemotherapeutic agents, statins	**1A/*1B*	**1A/*1A*	**1B* may influence prostate cancer
CYP3A5	Immunosuppressive drugs, protease inhibitors, statins	**3/*3*	**3/*3*	**3* is nonfunctional because of a splicing defect

Ng et al. (2008) *Clin Pharmacol Ther.* **84:** 306-309

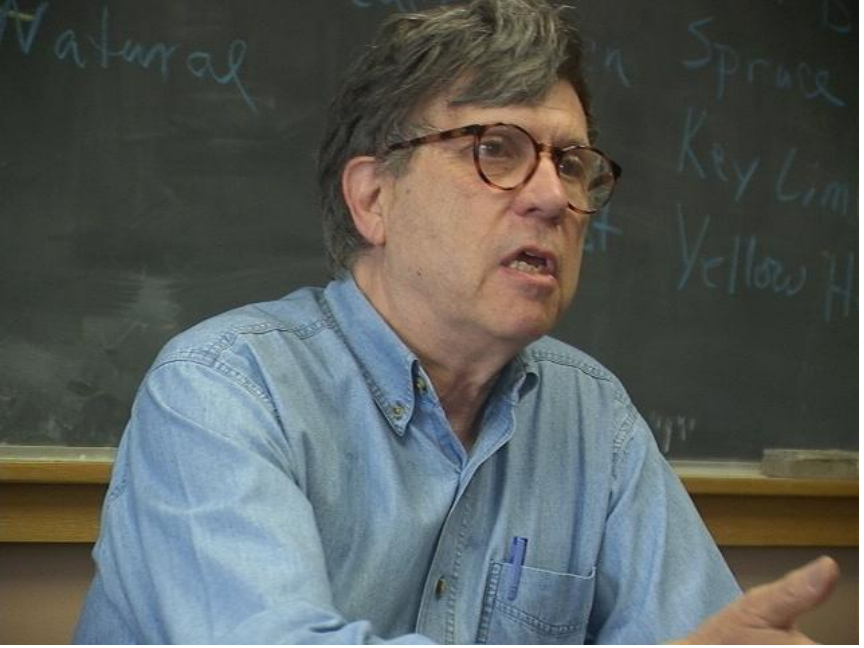

PRECISION
Targeted Therapies
Based on
Molecular Diagnostics
PERSONALIZED
Prevention and Treatment based
on Environment, Lifestyle,
and Genes
Precision Medicine
is science – a new wave of
evidence-based medicine
Personalized Medicine
is a practice – managing a
patient's care more
holistically

Precision medicine is "an emerging approach for disease treatment and prevention that takes into account **individual variability in genes, environment, and lifestyle for each person**." The new GHR primer stresses that, although the term *precision medicine* is relatively new, the concept has existed in different areas of medical practice for a long time.



Ma…. c’è un ma!

Le razze escono dalla porta ma rientrano dalla ...finestra



Richard Lewontin
1929

Human Diversity, 1982

Non vi è praticamente alcun aspetto della variazione tra esseri umani che non sia influenzato in qualche modo dall'organizzazione sociale che caratterizza la nostra specie.

Anche le differenze nell'andamento delle malattie e della mortalità sono caratteristiche di gruppi socialmente definiti.

Esistono le razze umane ?

Esistono differenze biologiche tra gruppi umani riconducibili a categorie razziali?

Mortalità infantile 1995-2004 (Gravlee, AJPA 2009)

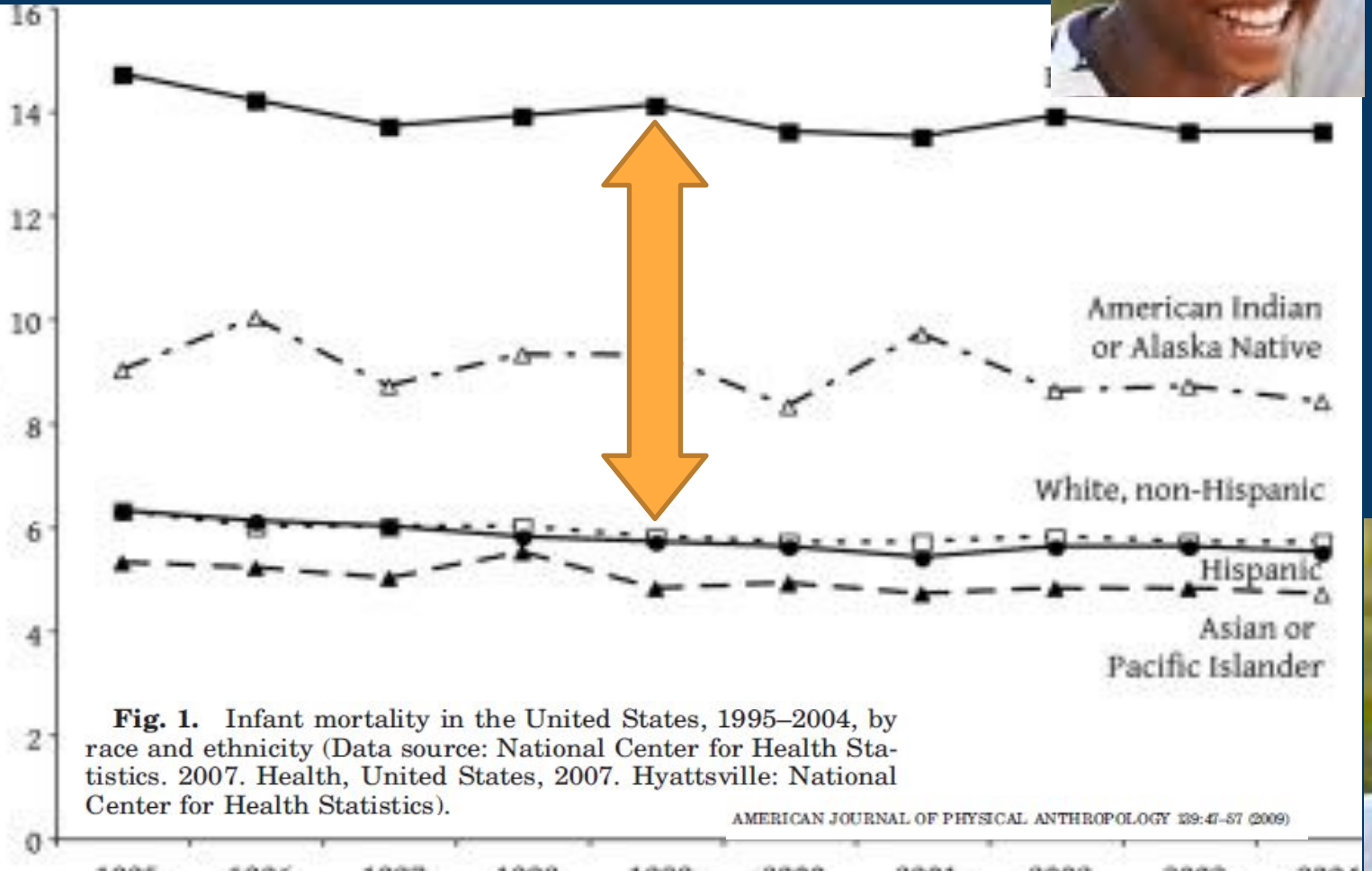


Fig. 1. Infant mortality in the United States, 1995–2004, by race and ethnicity (Data source: National Center for Health Statistics. 2007. Health, United States, 2007. Hyattsville: National Center for Health Statistics).

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Aspettativa di vita 1995-2004 (Gravlee, AJPA 2009)

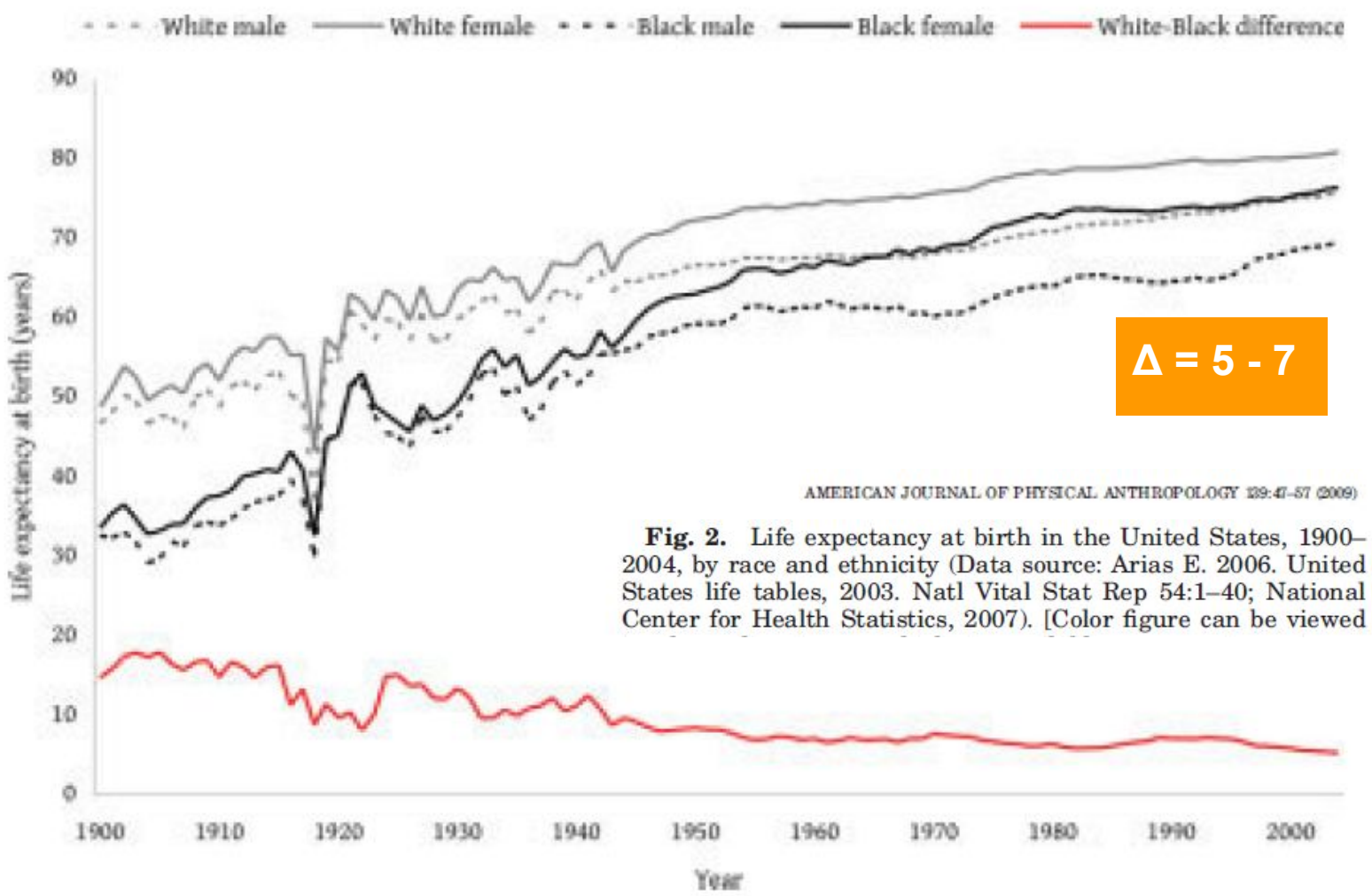

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Fig. 2. Life expectancy at birth in the United States, 1900–2004, by race and ethnicity (Data source: Arias E. 2006. United States life tables, 2003. Natl Vital Stat Rep 54:1–40; National Center for Health Statistics, 2007). [Color figure can be viewed

Le malattie cardiovascolari rappresentano la percentuale maggiore di differenza bianco-neri nella mortalità (34,0%)

I tassi di mortalità per età dovuti a diabete, setticemia, malattie renali e ipertensione sono più di due volte più alti tra gli afroamericani

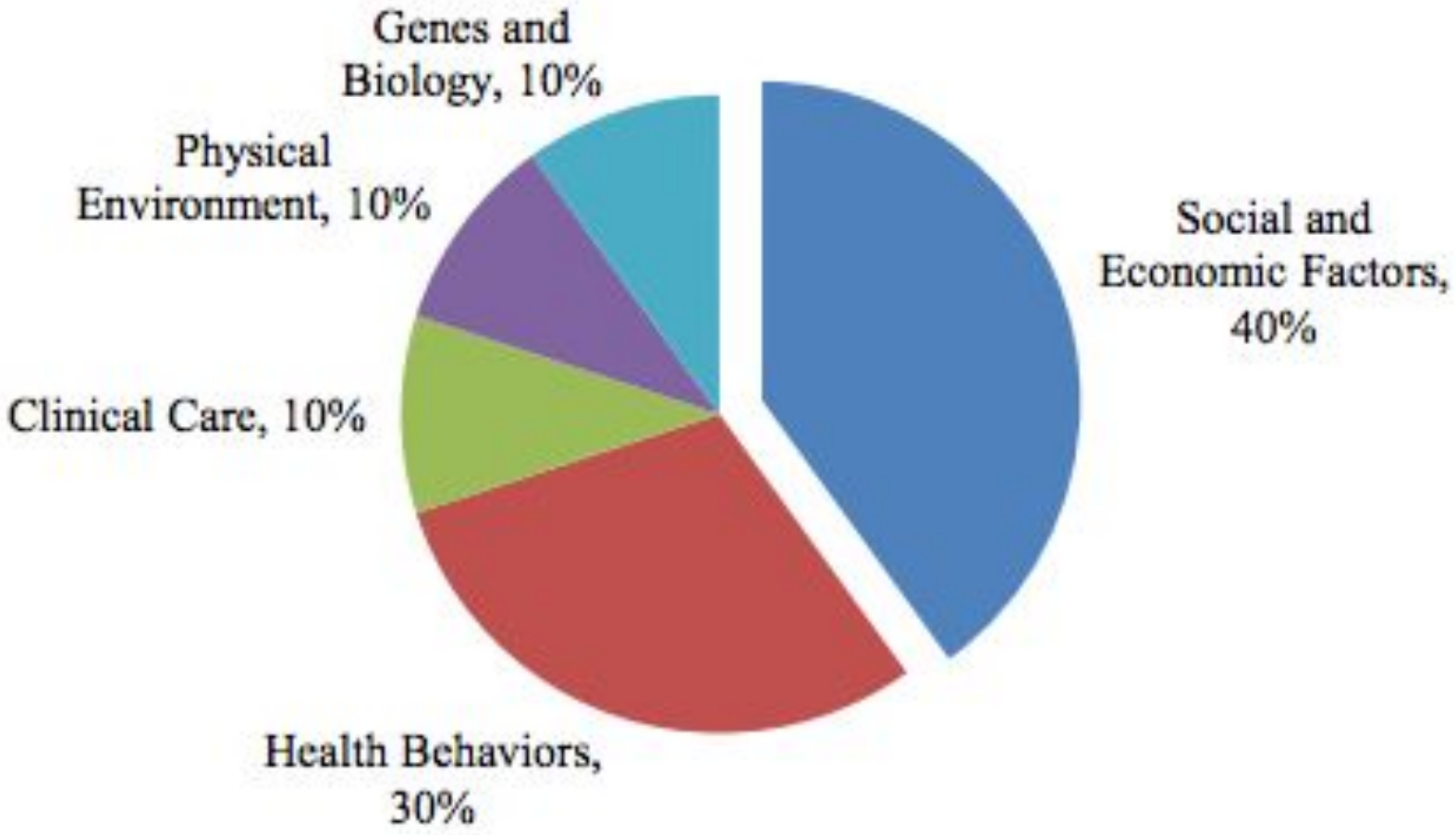
il tasso di mortalità corretto per l'età è superiore di oltre il 30% negli afroamericani

… ancora la percezione

“Racial” inequalities in health

1) socioeconomic status
2) health behaviors
3) psychosocial stress
4) Social structure and cultural context.
5) genetic factors.

The Determinants of Health



How race becomes biology

First, the sociocultural reality of race and racism has biological consequences for racially defined groups. Biology may provide some of the strongest evidence for the persistence of race and racism as socio cultural phenomena

Second, epidemiological evidence for racial inequalities in health reinforces public understanding of race as biology; this shared understanding, in turn, shapes the questions researchers ask and the ways they interpret their data —reinforcing a racial view of biology.

Races as a scientific fiction and a social fact