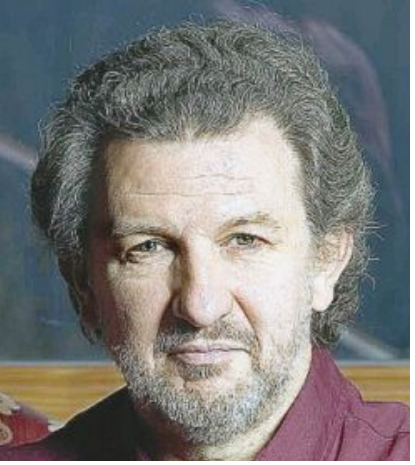
# Perché parlare ancora di razze...

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

Hannover Meso-dolicomorfo

Cavallo Arabo Mesomorfo

Frisone Meso-brachimorfo

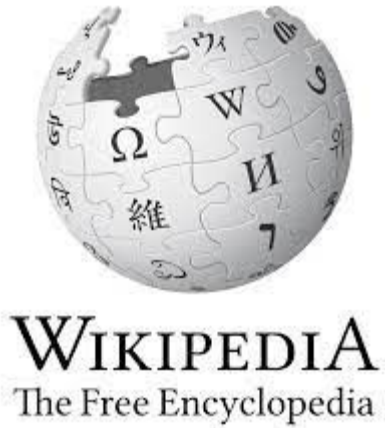
Purosangue Inglese

Dolicomorfo

Shire Brachimorfo

# 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

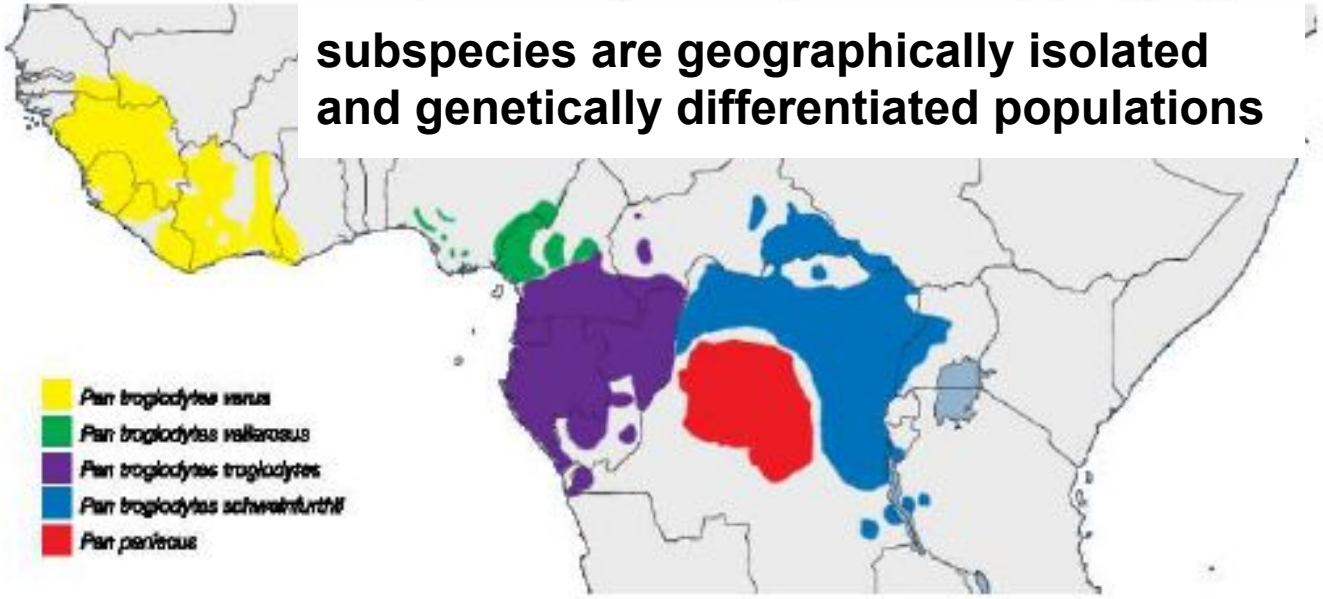
unità

- discrete
- esclusive
- omogenee

*sottospecie

# Esistono in **natura!**

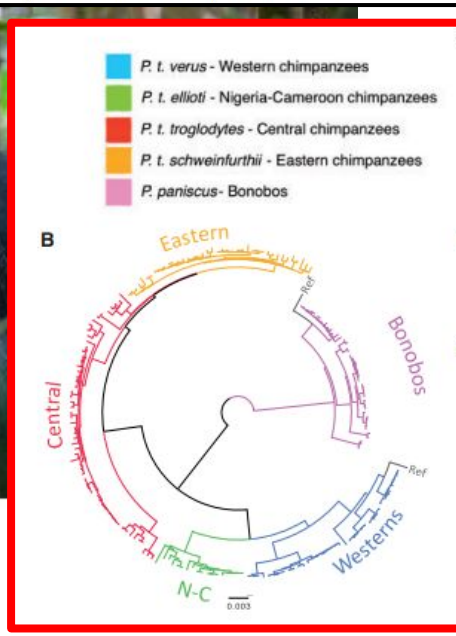
**subspecies are geographically isolated and genetically differentiated populations**



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,*]

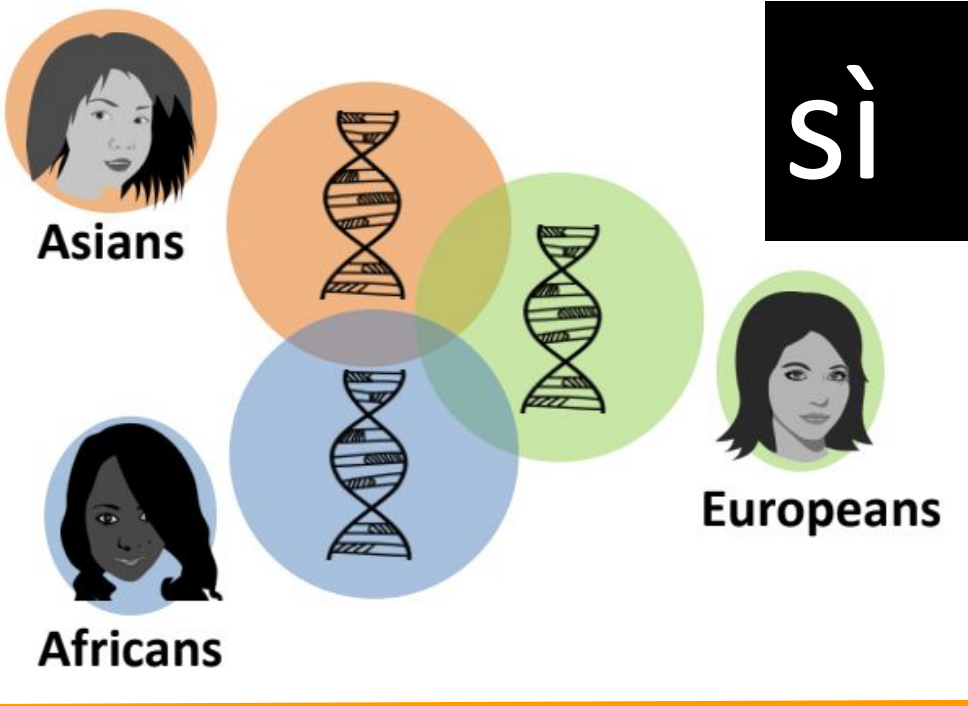



## Abstract

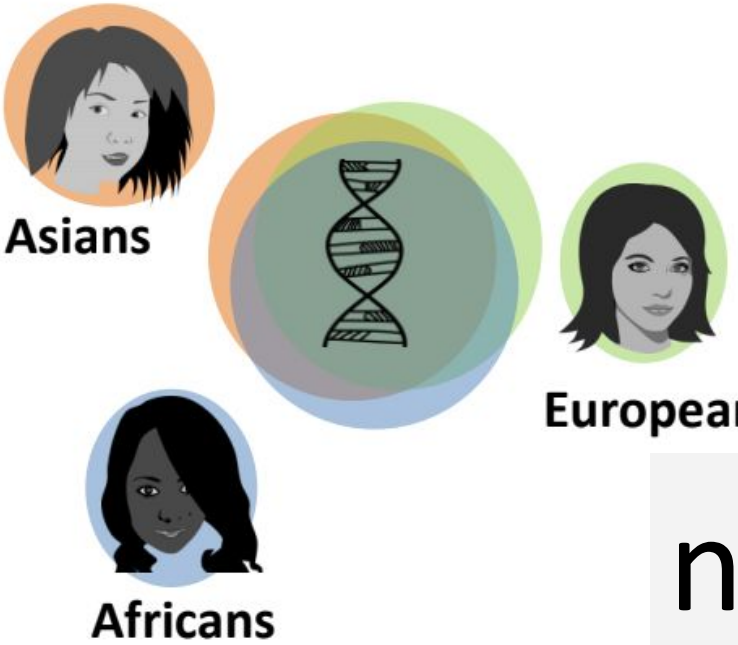
The genus *Pan* is the closest genus to our own and it includes two species, *Pan paniscus* (bonobos) and *Pan troglodytes* (chimpanzees). The later is constituted by four subspecies, all highly endangered. The study of the *Pan* genera has been incessantly complicated by the intricate relationship among subspecies and the statistical limitations imposed by the reduced number of samples or genomic markers analyzed. Here, we present a new method to reconstruct complete mitochondrial genomes (mitogenomes) from whole genome shotgun (WGS) datasets, mtArchitect, showing that its reconstructions are highly accurate and consistent with long-range PCR 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 populatior

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

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



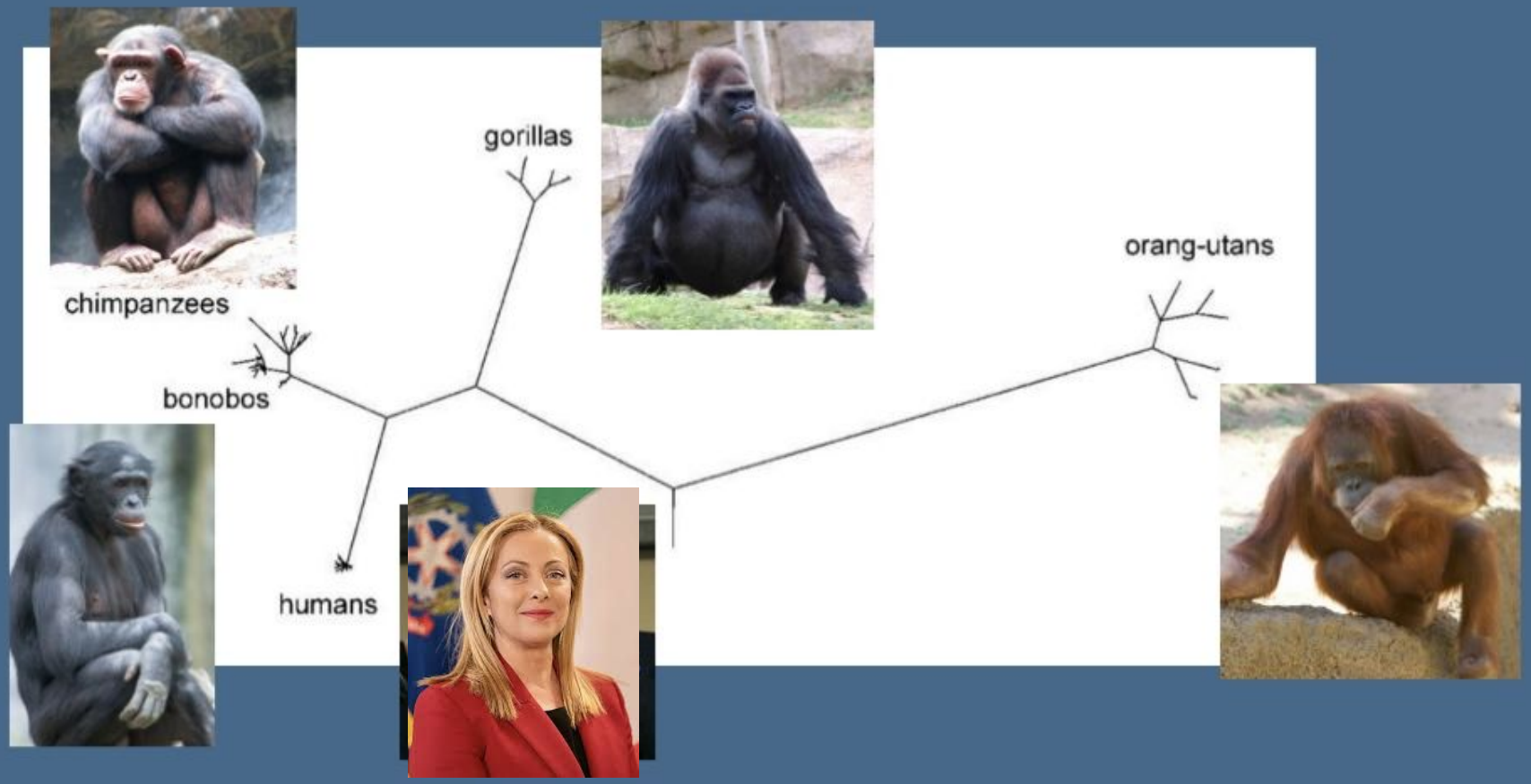

sì




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).

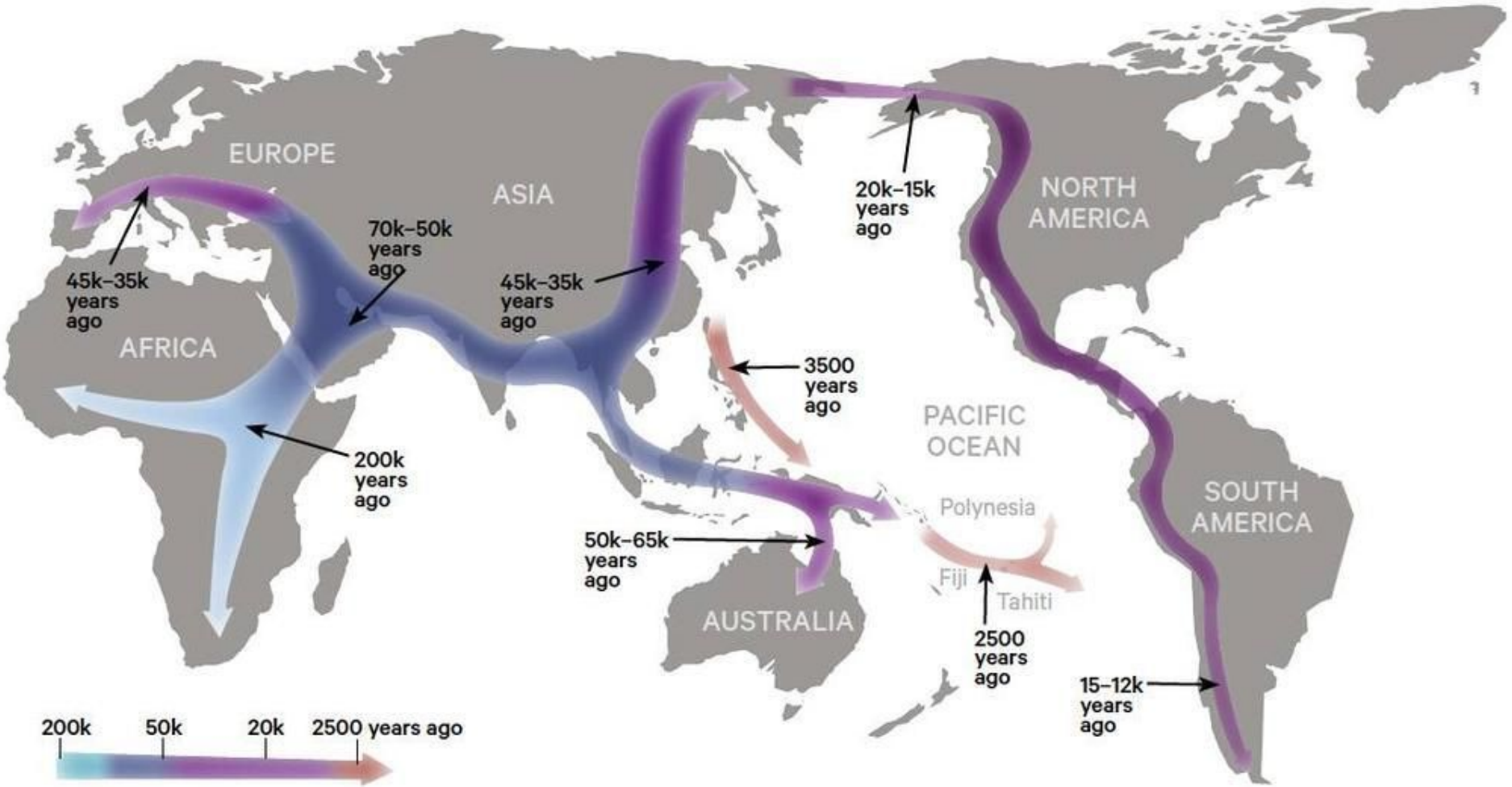
# 1 Extent of diversity compared

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

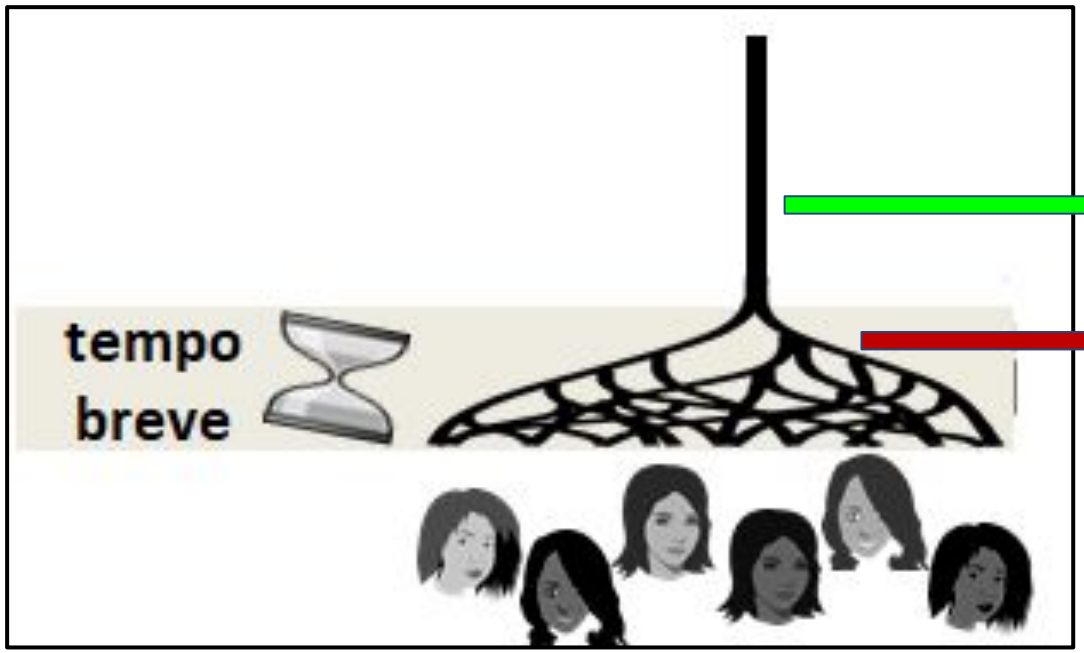
| Locus | Chimpanzee vs. human | Bonobo vs. human |
|---|---|---|
| Xq13.3 | 3-fold greater | n.d. |
| mtDNA | 3–4-fold greater | Greater |
| Y chromosome | Greater | n.d. |
| MHC class I genes | Greater, but less in HLA-A comparison | n.d. |
| ABO blood group genes | 2–3-fold less | 4–7-fold less |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

# 2 Extent of Time since divergence

# Le più antiche migrazioni umane



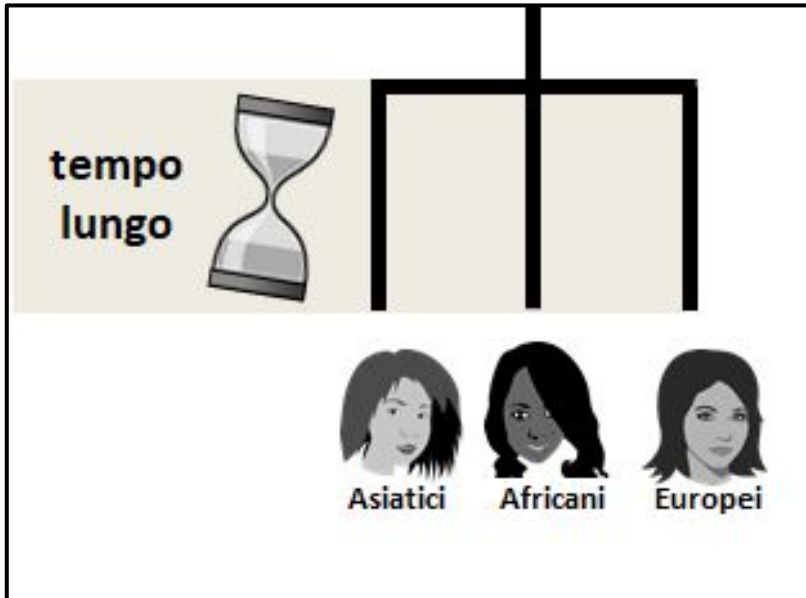
and 44 bonobo individuals, with a proportional contribution from all chimpanzee subspecies. We estimated the separation time between chimpanzees and bonobos around 1.15 million years ago (Mya) [0.81–1.49]. Further, we found that under the most




60-80 KYA
H. sapiens emergence

65 KYA
H. sapiens expansion

# 2 Extent of Time since divergence



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

# 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 $\pi_b$ Values, above and below the Diagonal, Respectively, for Each Pairwise Comparison

| $\pi$ 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 | |

# 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**

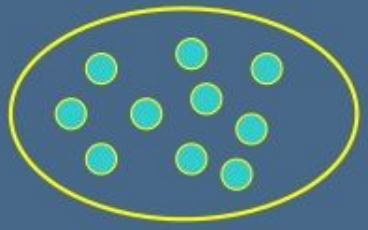
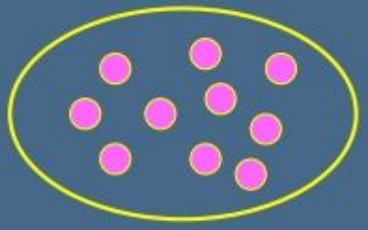
International HapMap Consortium 2006

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

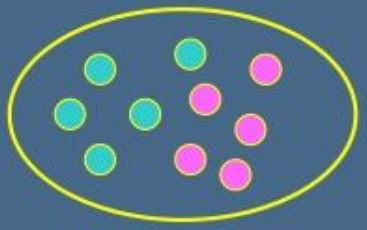
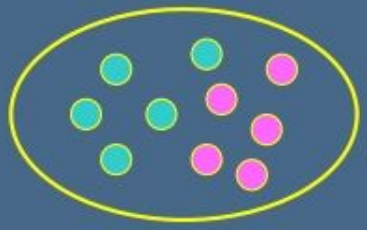
- dentro le popolazioni
- tra le popolazioni
- tra i gruppi di popolazioni (continenti, “razze”)

# Genetic variances within and between populations

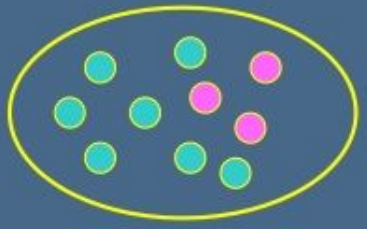
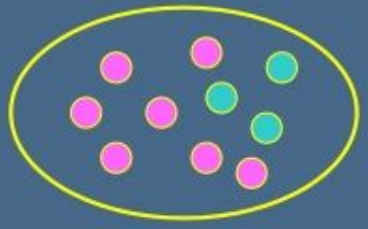
Population 1 Population 2 variance between pops.

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% |

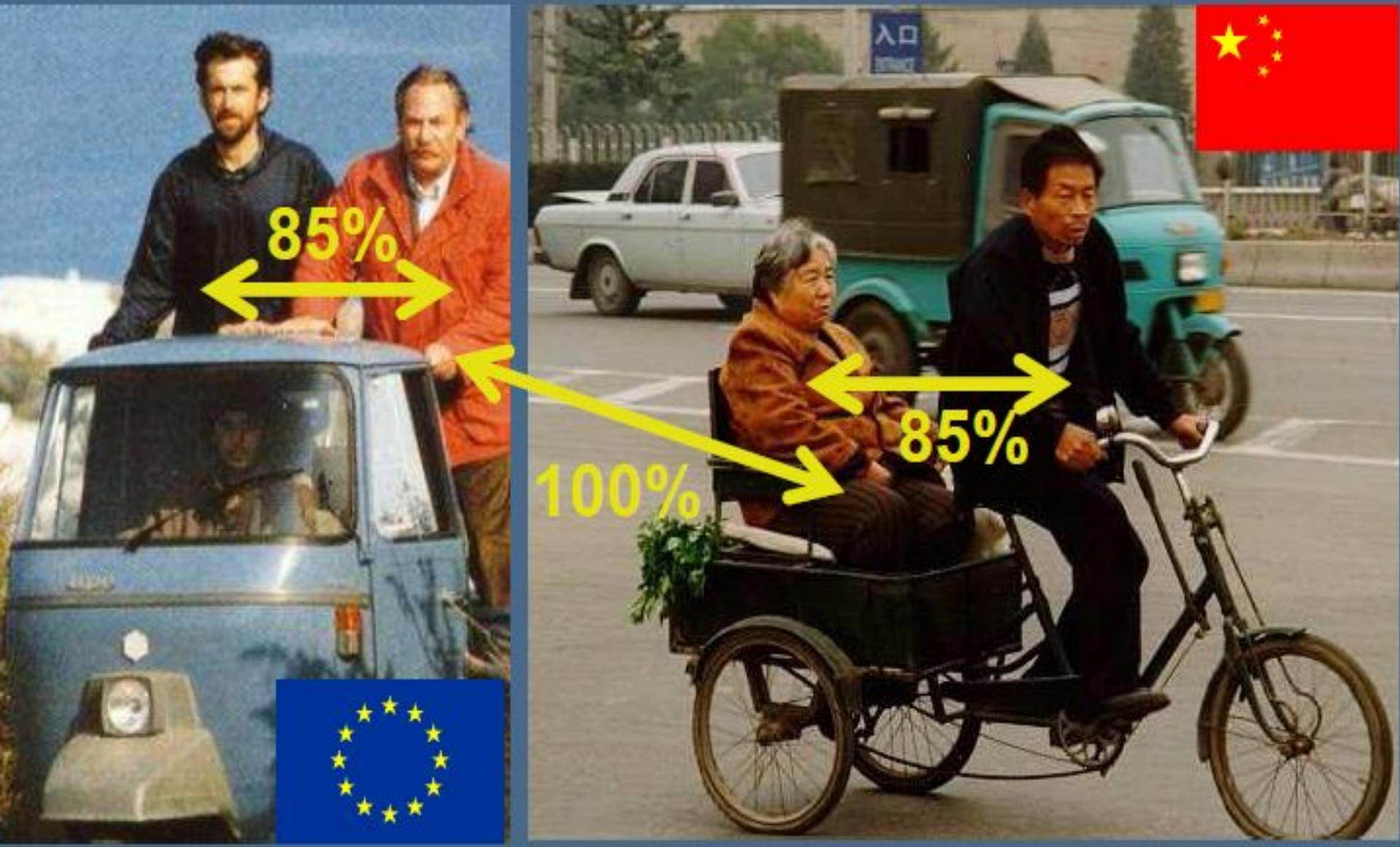
85% 5% 10%

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

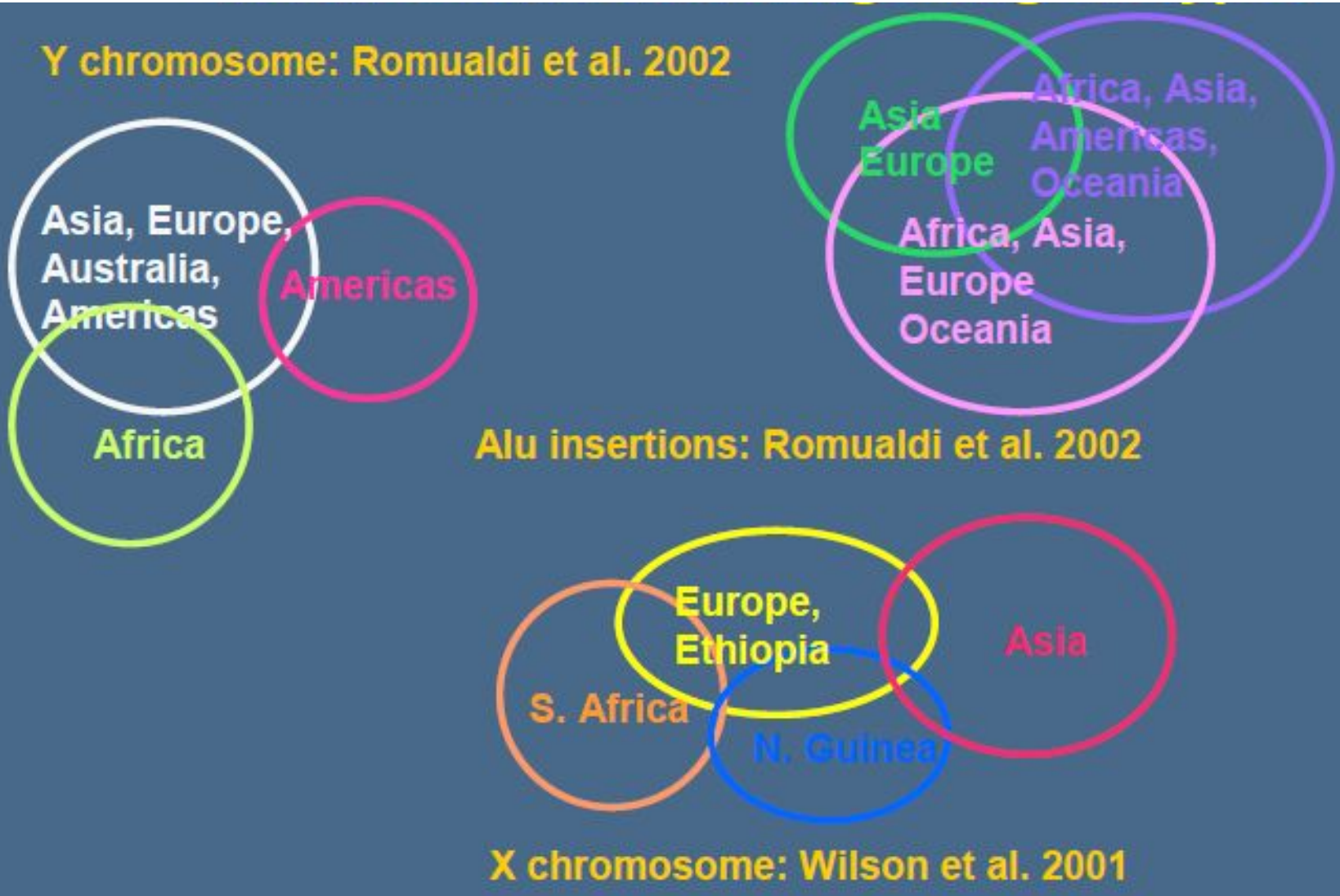
| Gene Identification Method | EST Alignment | Predicted | mRNA Alignment |
|---|---|---|---|
| Number of Genes | 3,295 | 11,972 | 17,708 |
| Exons/Gene (Avg) | 4 | 5 | 12 |
| Exon Length (Avg) | 440 | 158 | 226 |
| Intron Length (Avg) | 5,605 | 10,512 | 5,478 |
| mRNA Length (Avg) | 2,127 | 820 | 2,741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

Ma la partita non è ancora chiusa

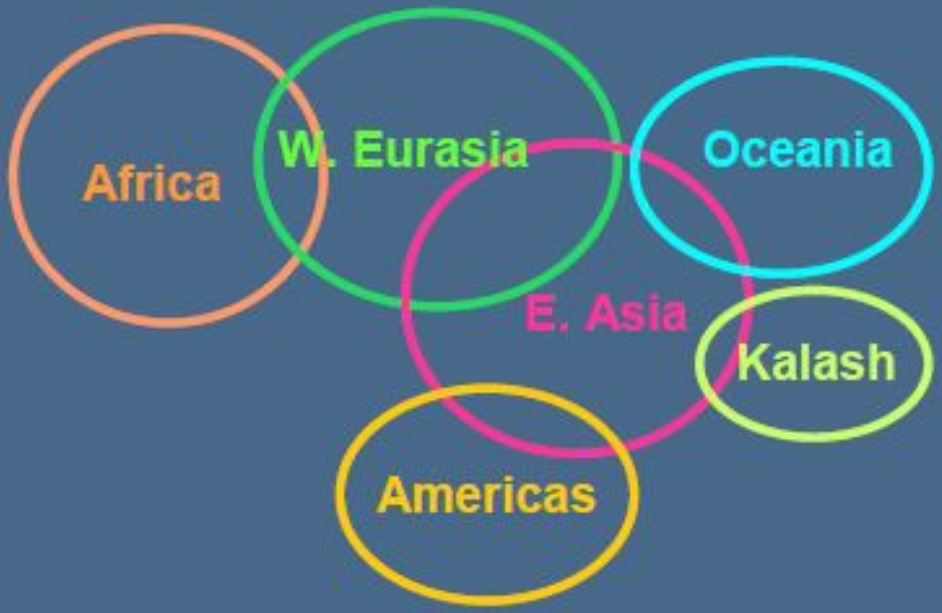
La 1/10.000 parte di 3.200.000.000 è 320.000 nucleotidi

**Troviamo nei 300KB segni coerenti di differenziazione in razze?**

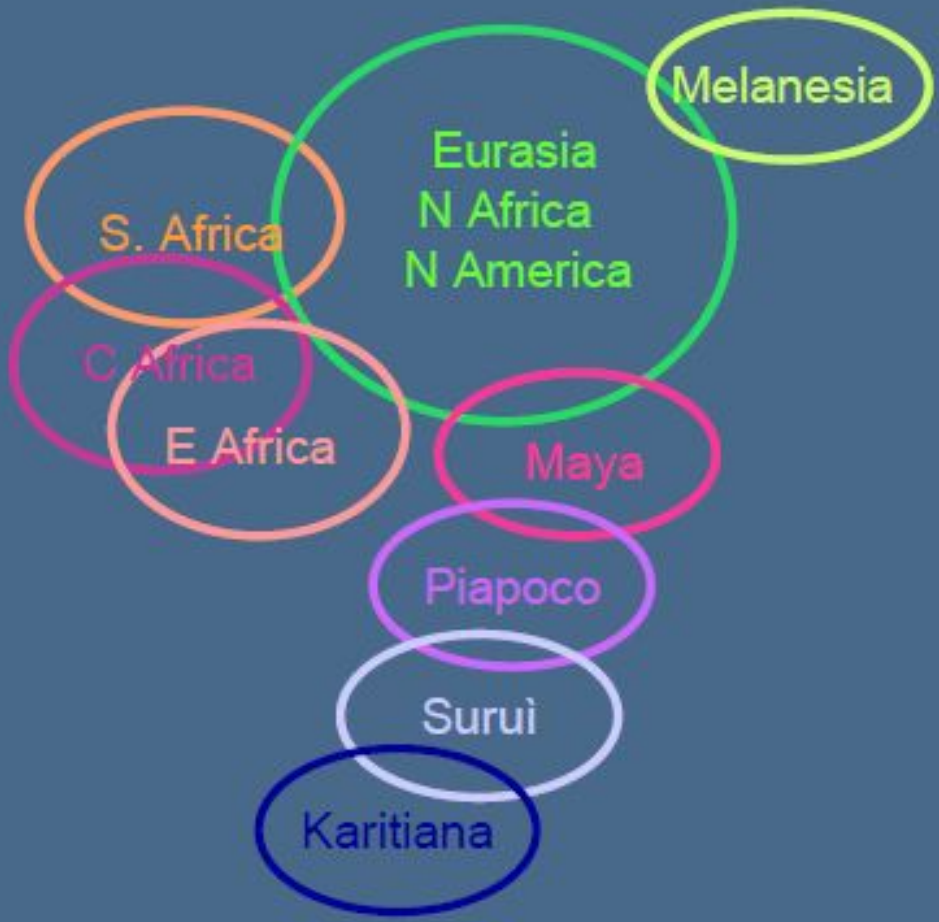
# Evidenze genetiche di raggruppamenti razziali ?



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



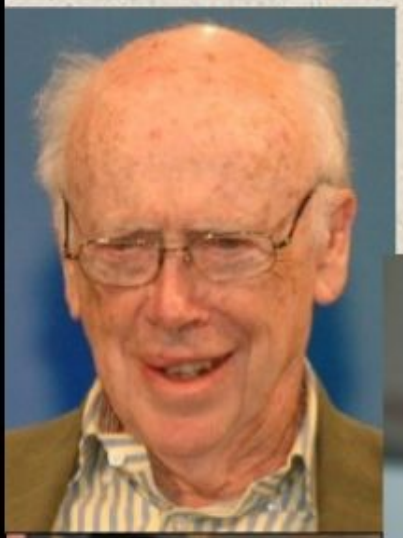

377 STR loci: Rosenberg et al. 2005

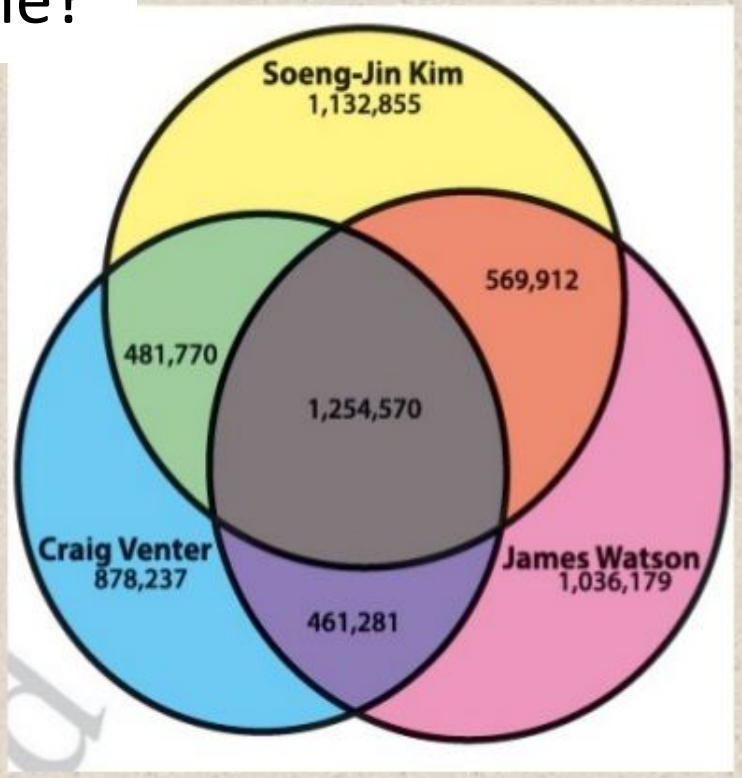



377 STR loci: Barbujani and Belle 2006

# Un problema di scarsa risoluzione?

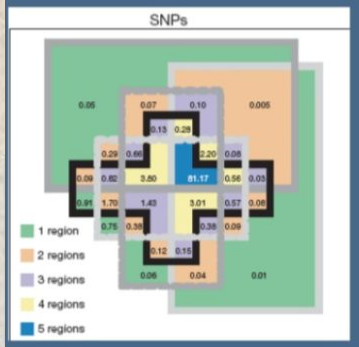
very large






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

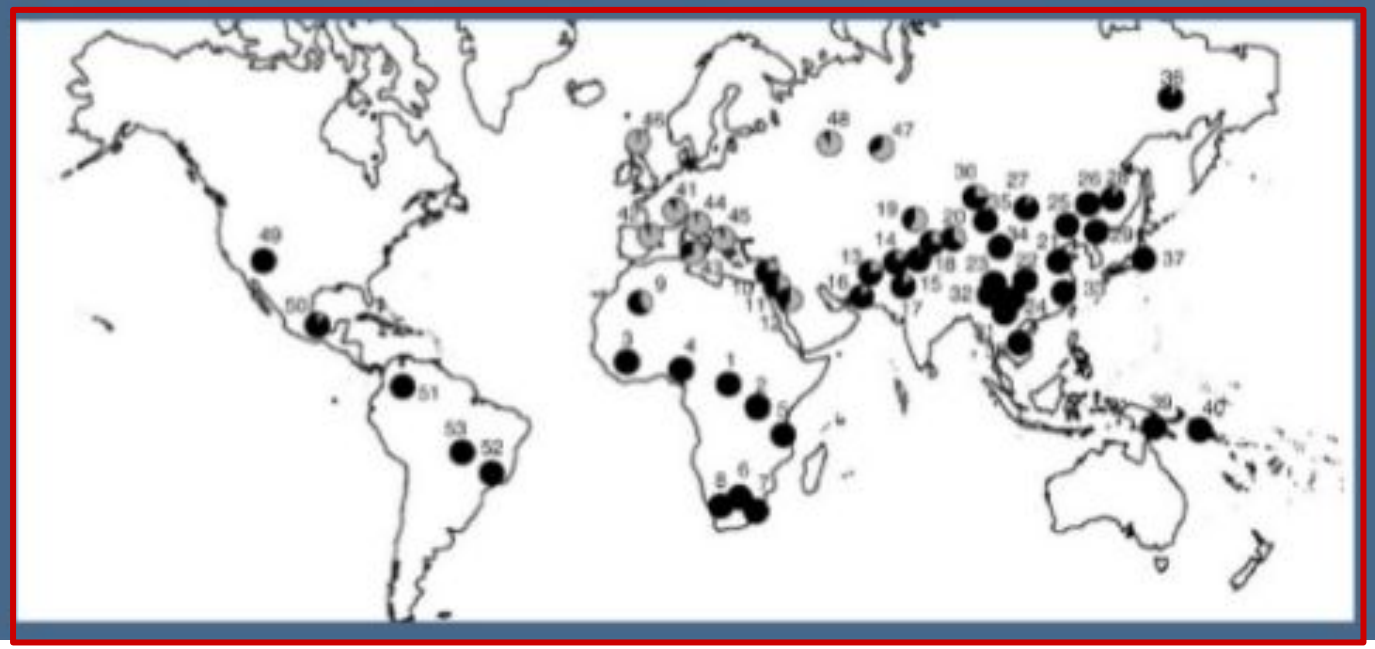



81% of SNPs cosmopolitan.

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**

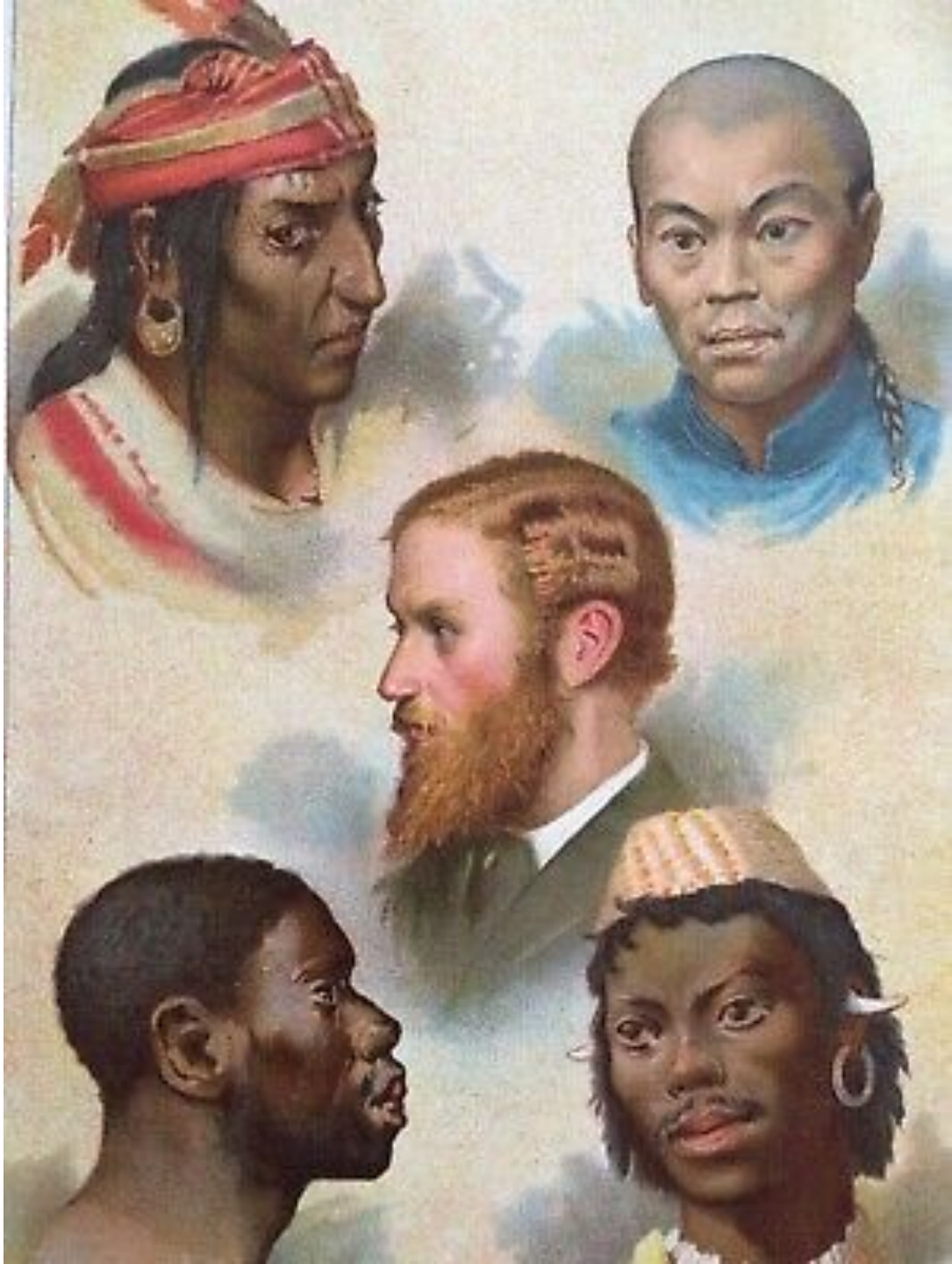
Agouti signaling protein, chromosome 20q11

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

**SLC45A2**

Membrane-assoc. transporter protein, chromosome 5

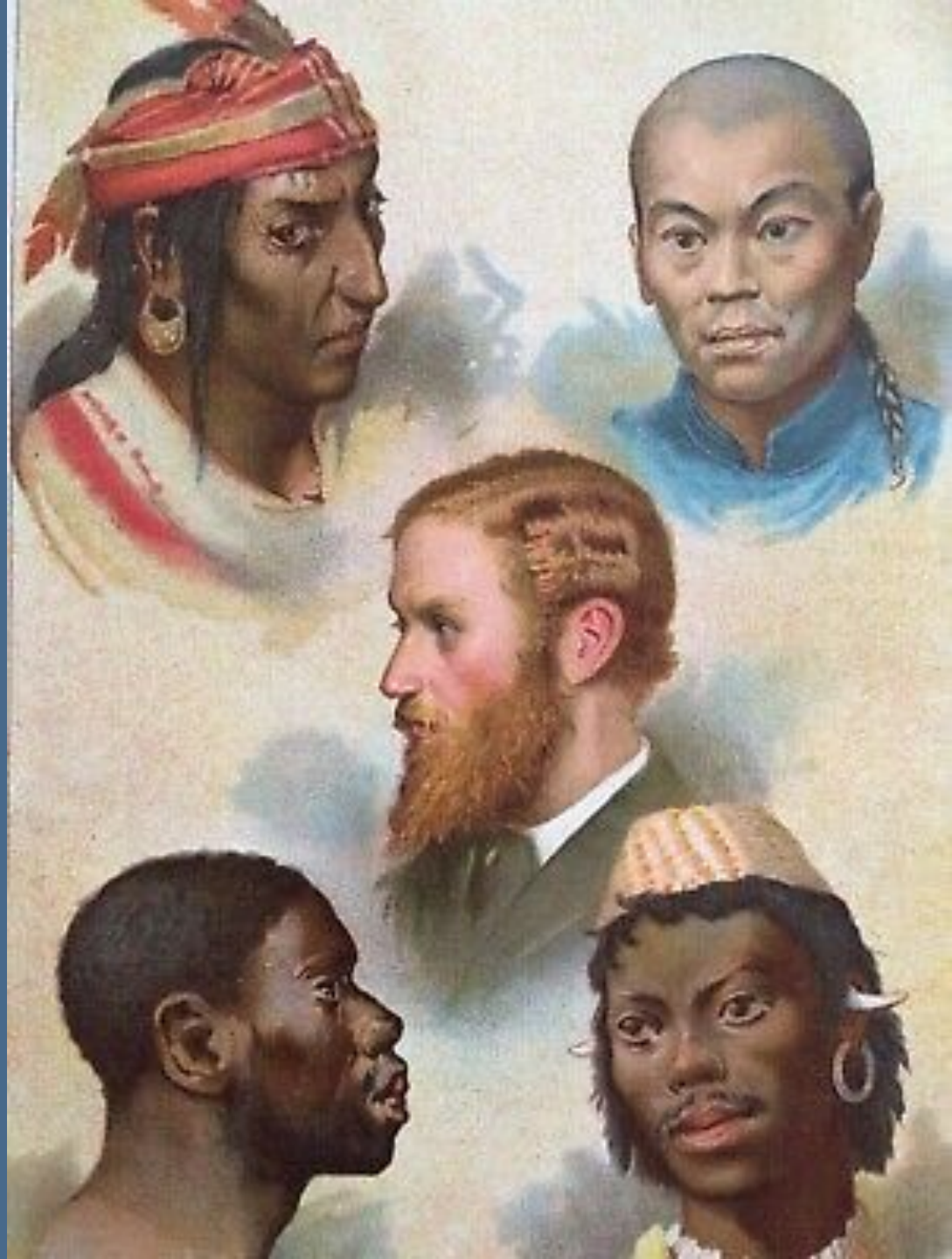
Ma perchè allora in passato (e anche oggi.. ) si è dato tanto credito al concetto di razza?



# WARNING

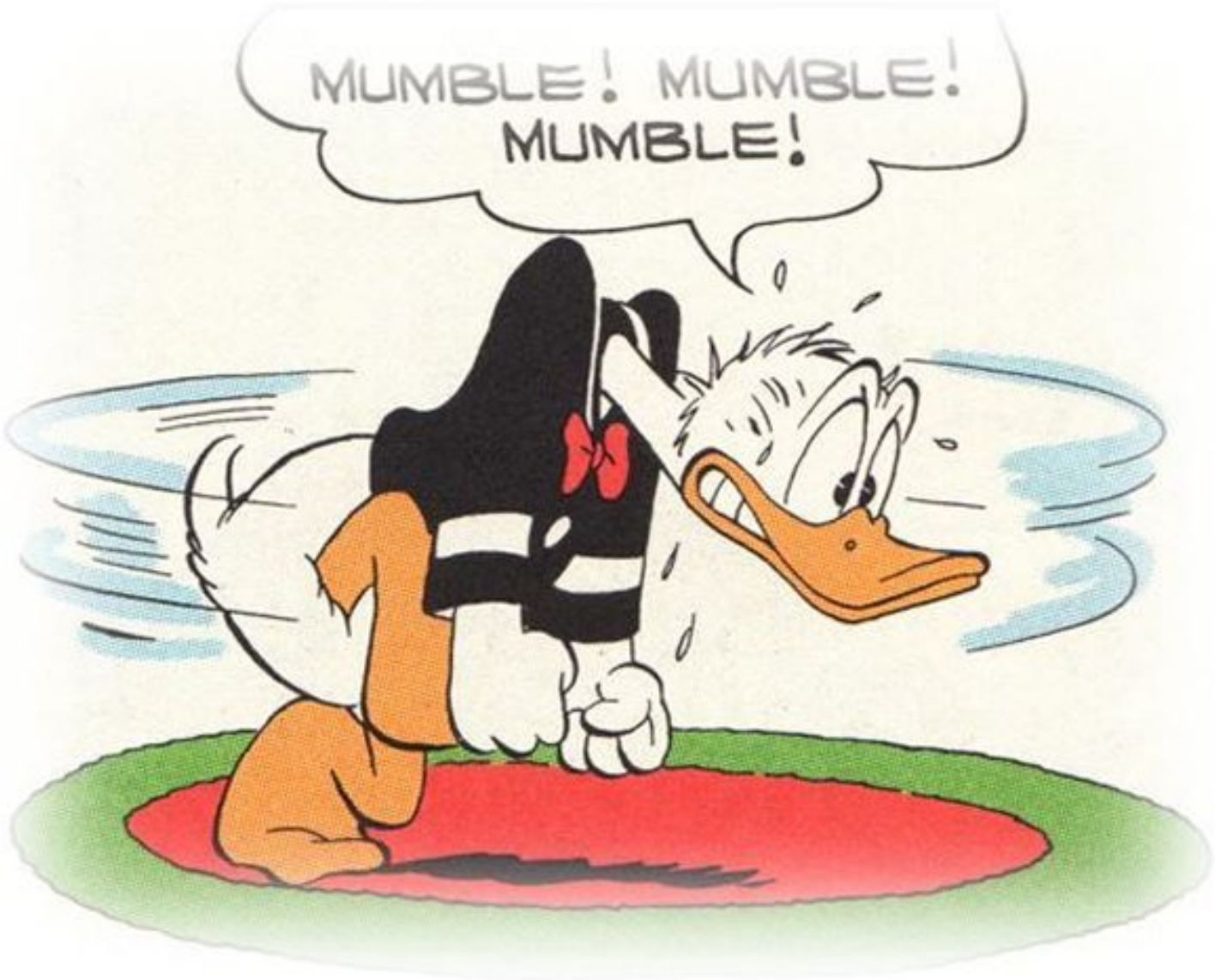
Sono il prodotto di più geni e dell'ambiente che può modificare la loro distribuzione (selezione naturale) ed espressione (statura).

Quindi
Omoplasia?
Convergenza adattativa?



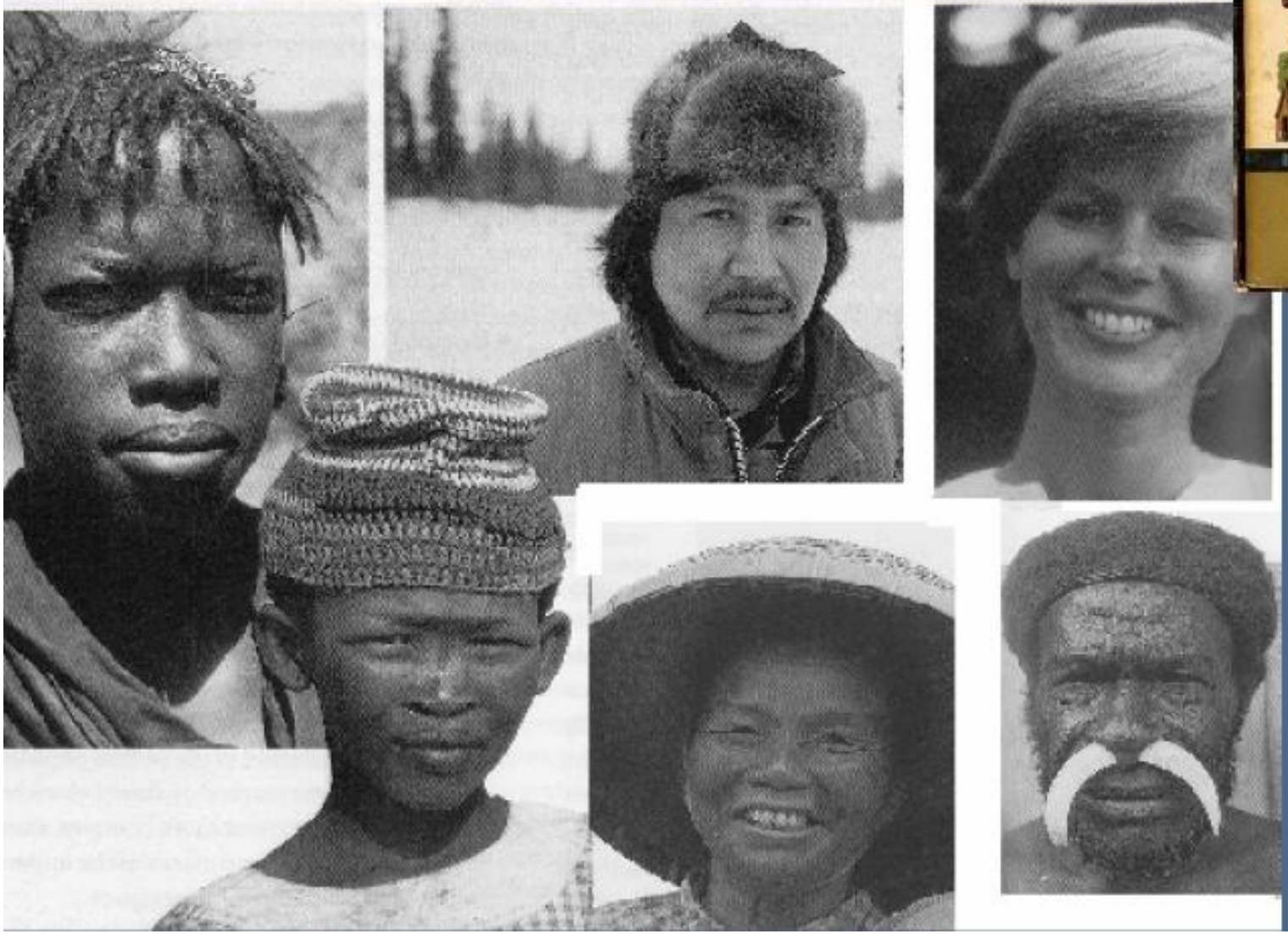
1. L’apparenza dei caratteri esterni inganna

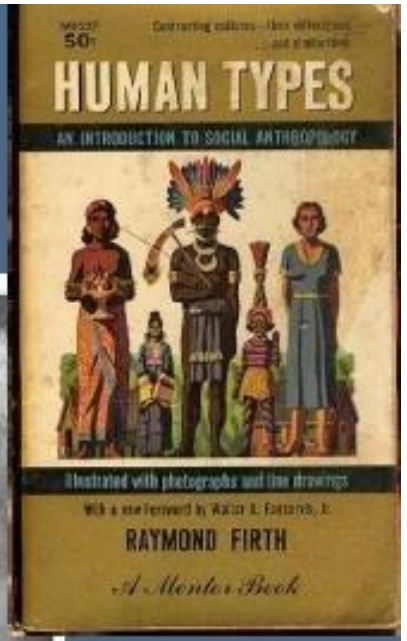
INDOVINA LA NAZIONALITA!


MUMBLE! MUMBLE!
MUMBLE!

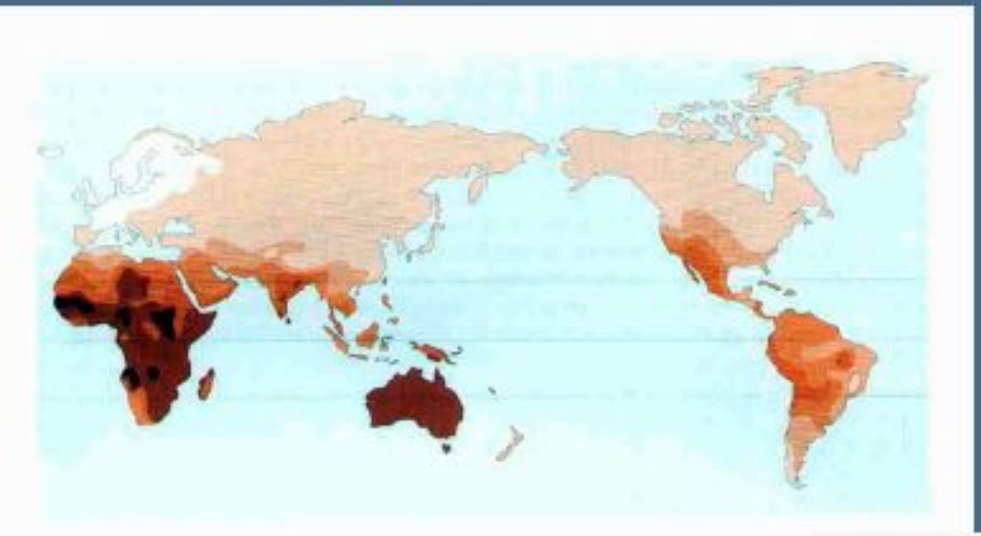
POLONIA! (sconsigliato a chi ha problemi di digestione)

# Gruppi discreti?





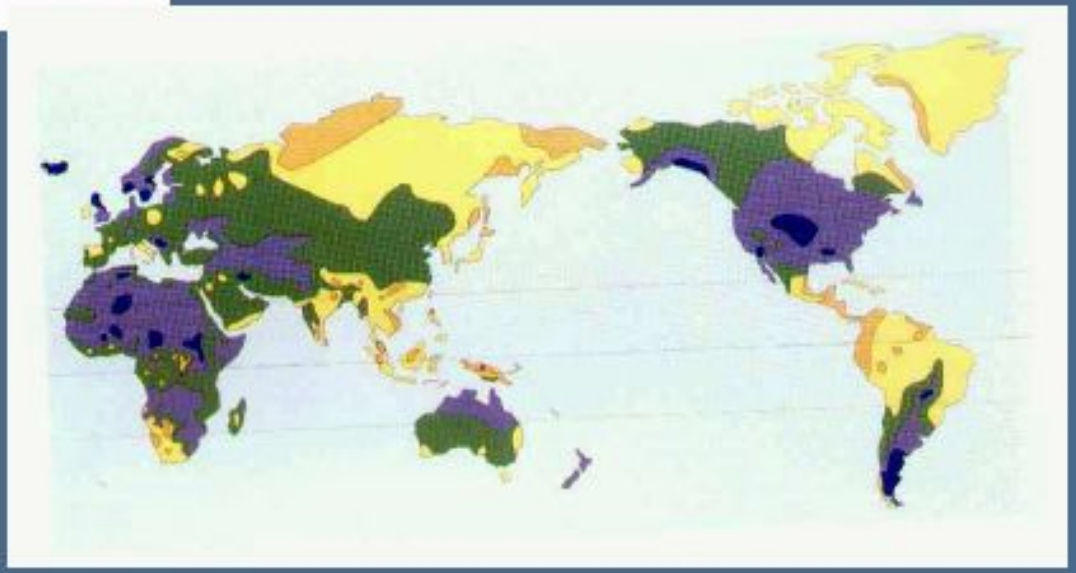
# Il guaio dei caratteri morfologici



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**

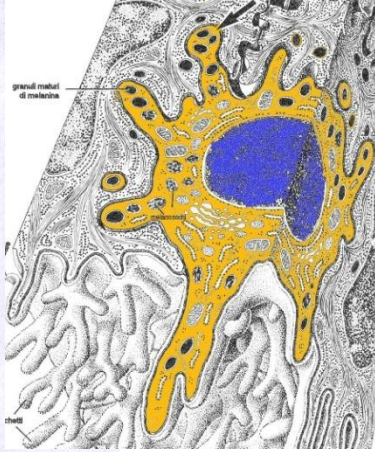
# Lo studio della morfologia porta a cataloghi razziali contrastanti

| | |
|---|---|
| Linneo (1735) | 4 (europeus, luridus, afer, americanus) [+2] |
| 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) |

# 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)

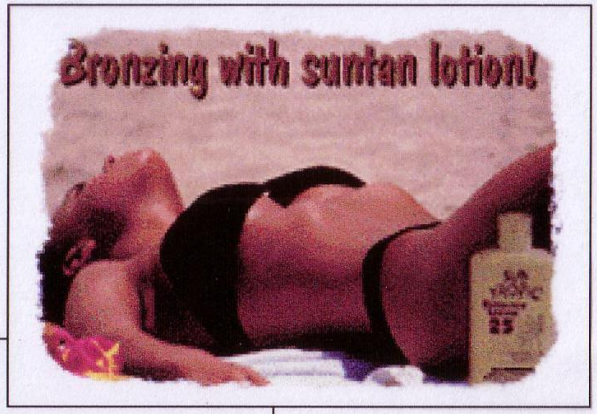
http://science.sciencemag.org/content/early/2017/10/11/science.aan8433

# 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:

tirosinasi + $O_2$ dopaossidasi + $O_2$

Tirosina → dopa → dopachinone

dopacromo → indolo-5,6-chinone → omopolimero **melanoproteina**

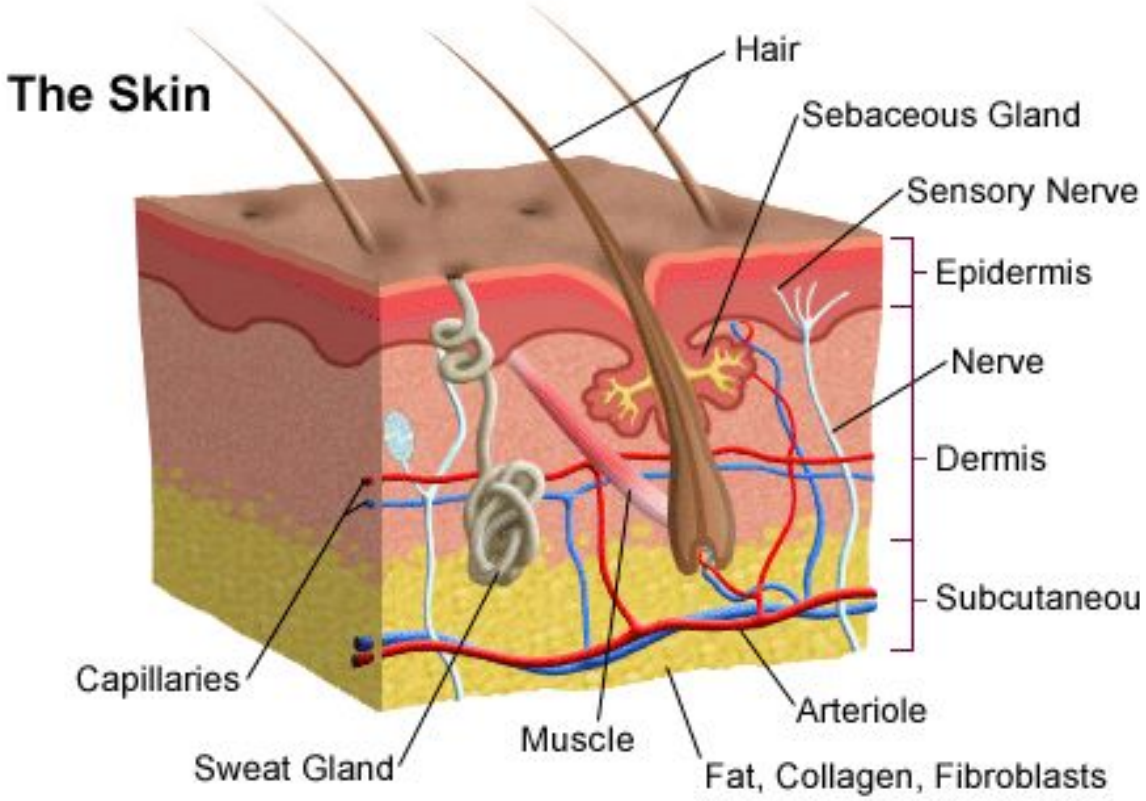
Cisteina o mercaptani

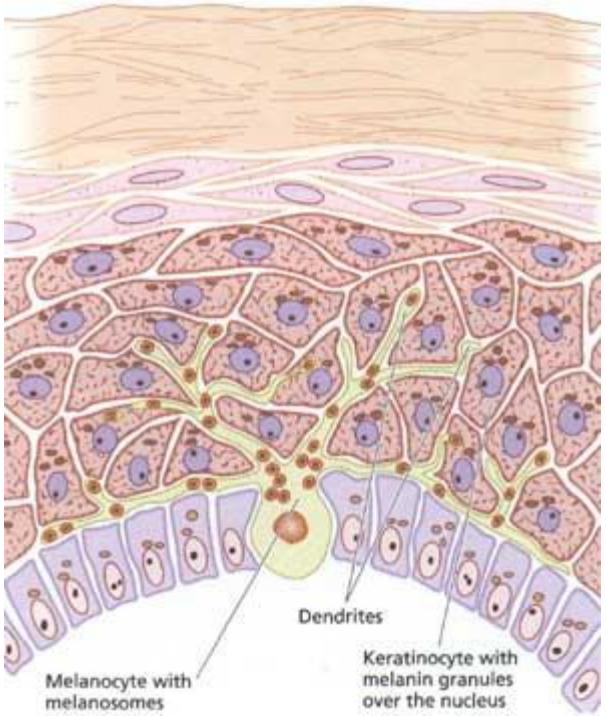
*Feomelanine*

*tricocromi*

Melanosomi ➡ dendriti del melanocita ➡ cheratinociti del'epidermide ⬇

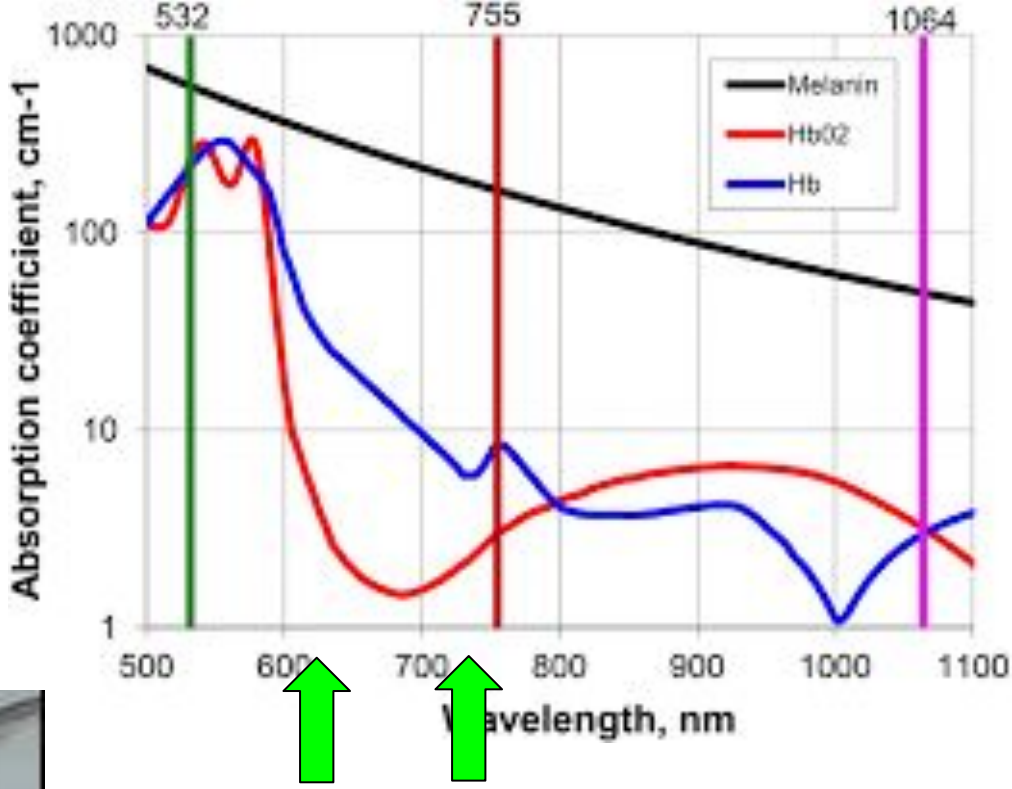
strati superficiali della pelle e bulbi piliferi

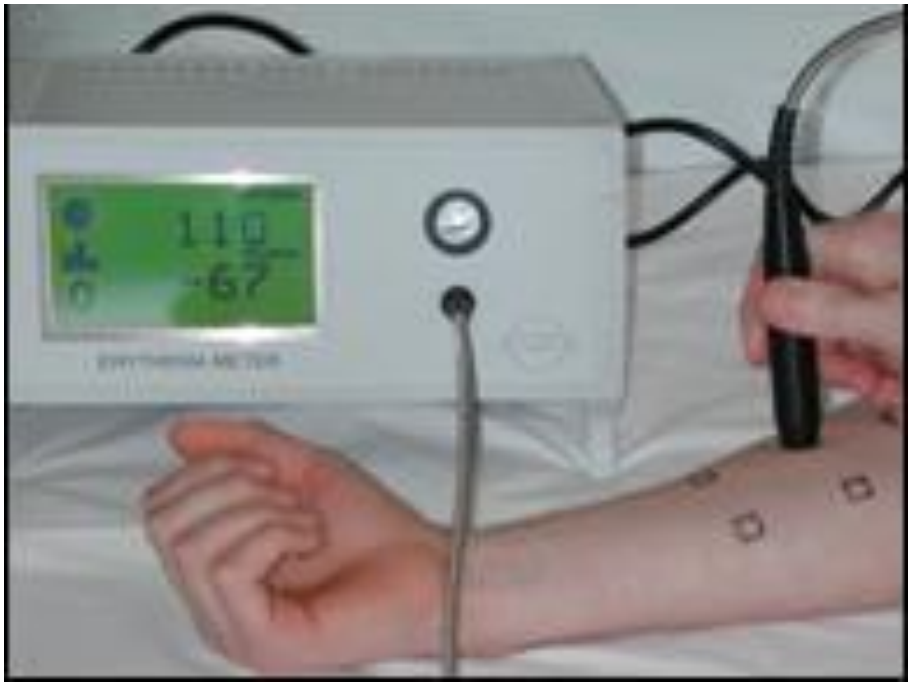


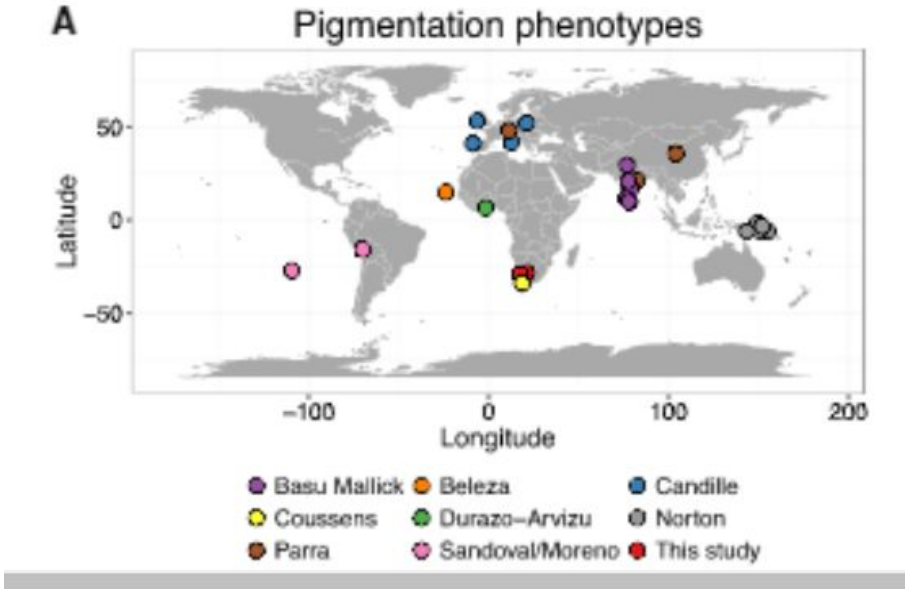

La melanina è contenuta all'interno dei **melanosomi** che possono essere presenti in uno spessore variabile dell'epidermide:

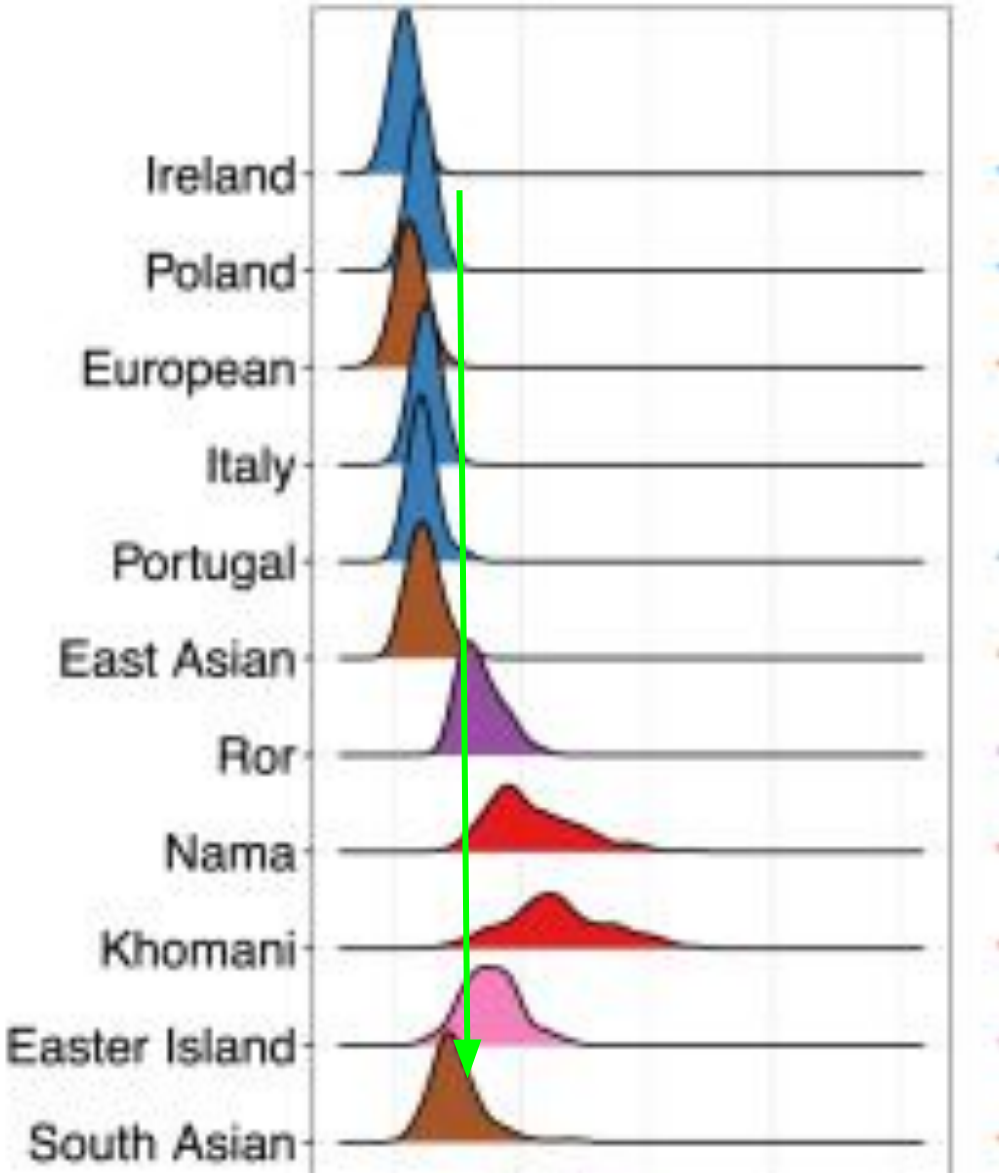
- **Epidermide germinativa**: strato più profondo dell'epidermide ed è sostenuto da una membrana basale che lo separa dal derma sottostante
- **Strato spinoso**
- **Strato granulare**


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

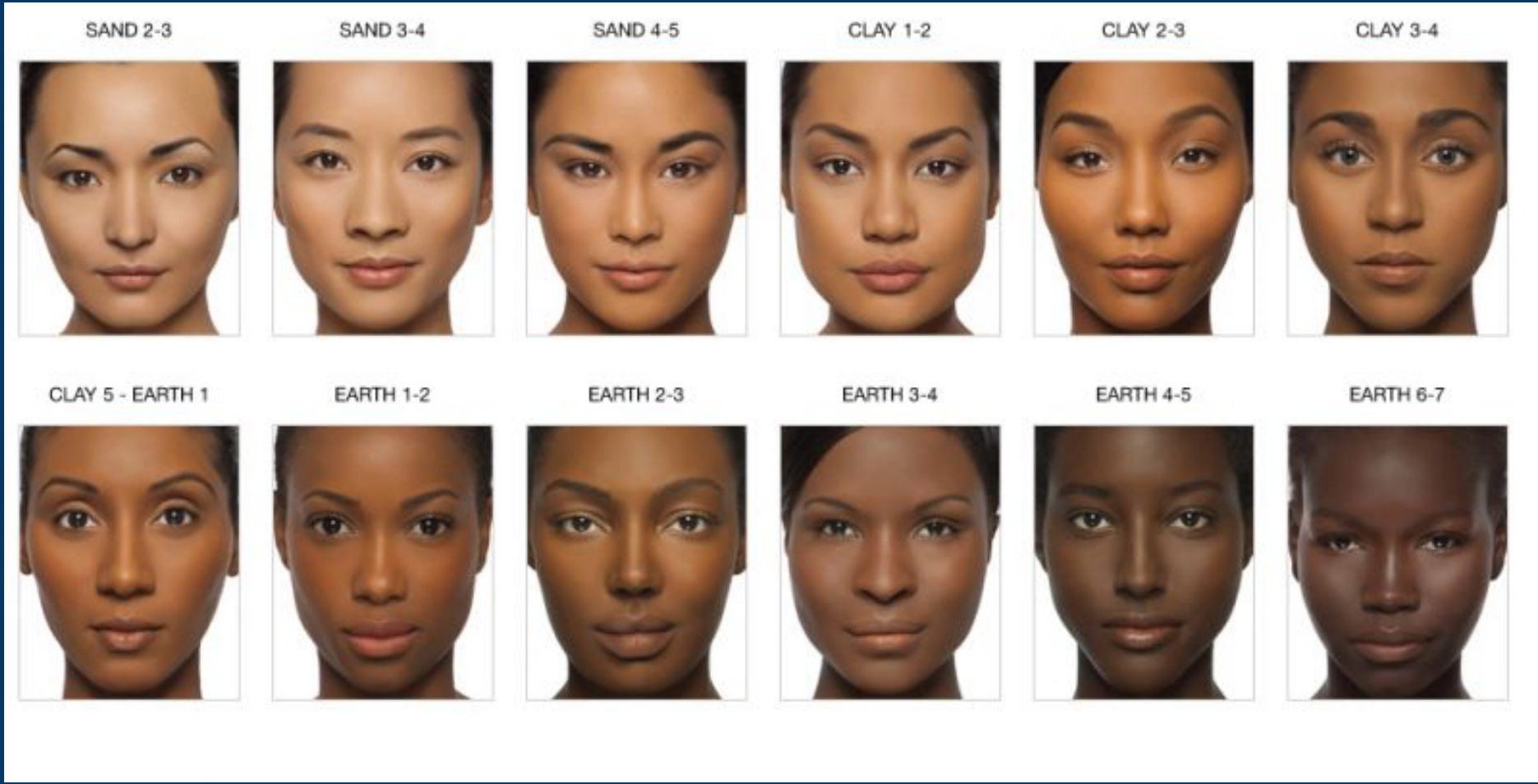



https://doi.org/10.1016/j.cell.2017.11.015

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?!



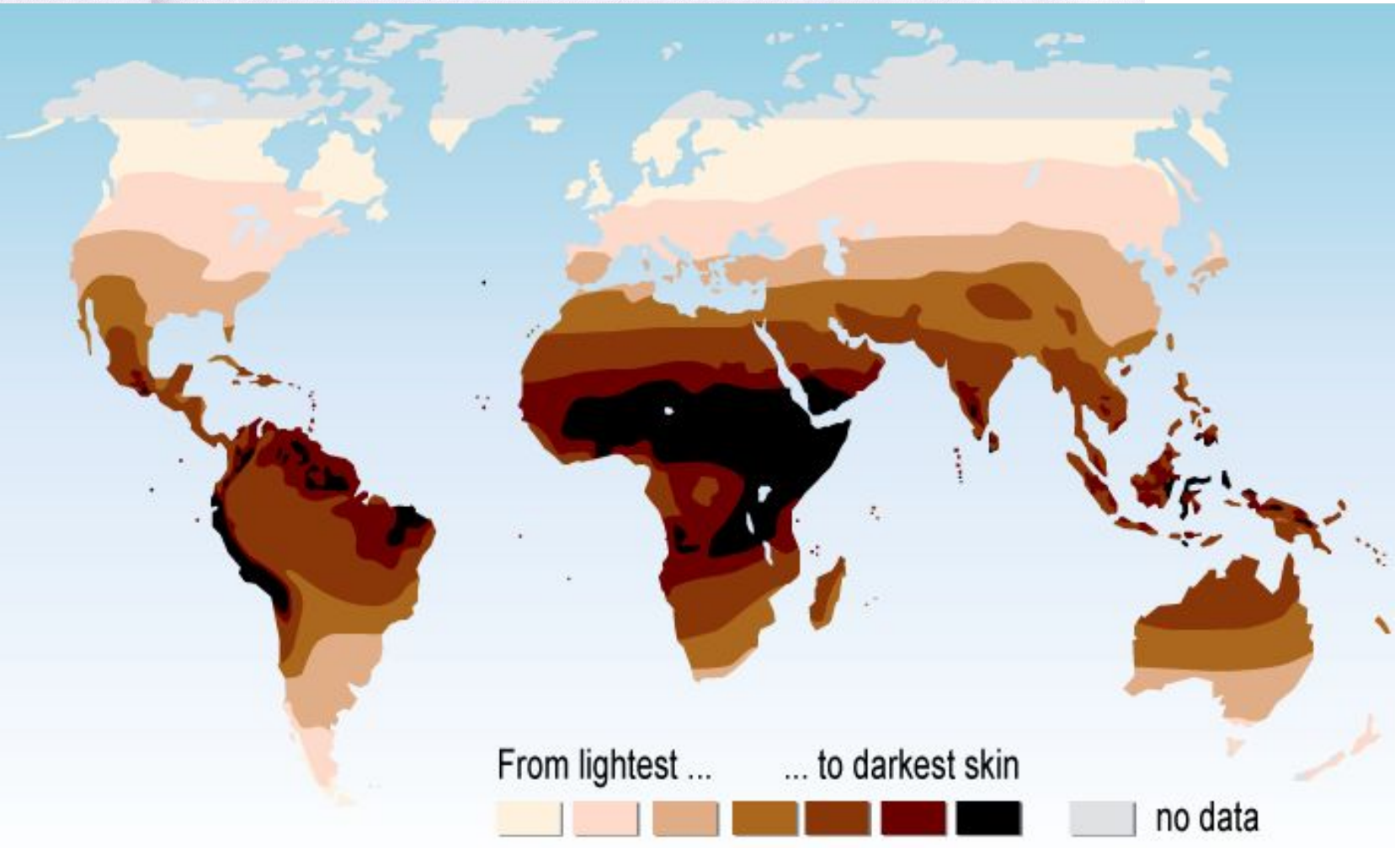
# Pigmentazione distribuzione

**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

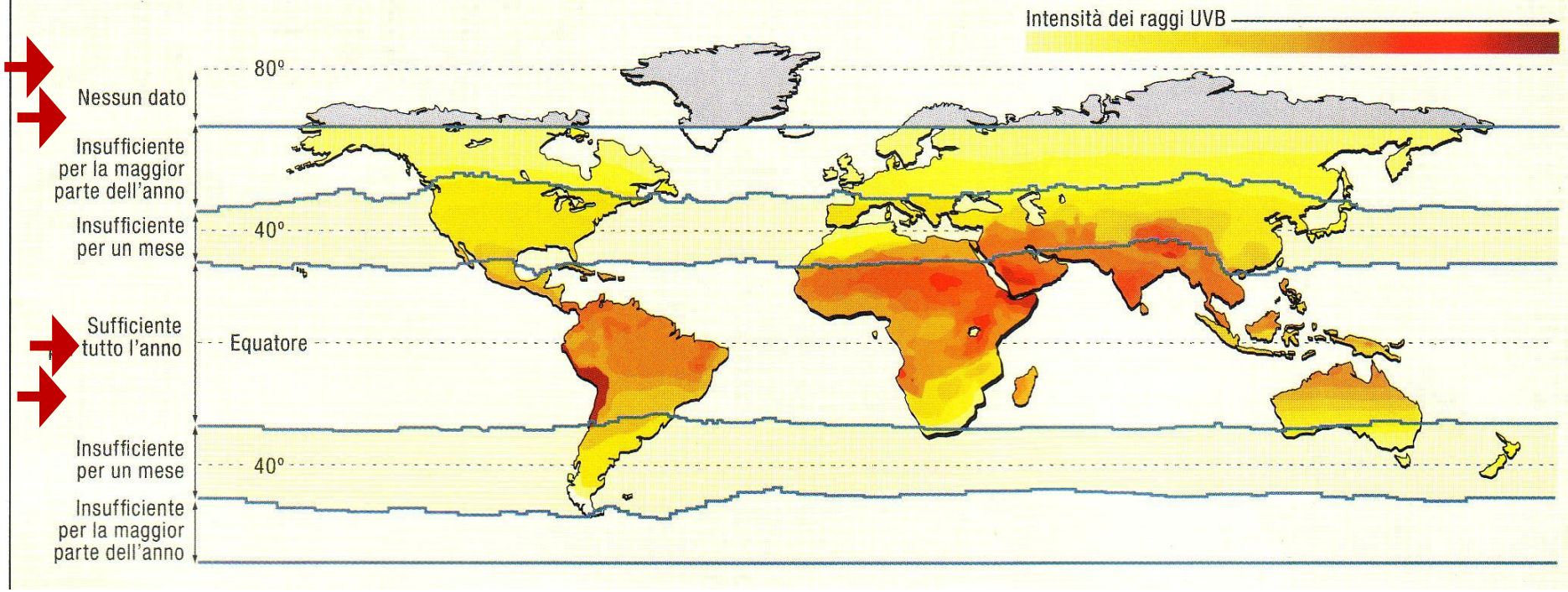
sì Acido folico

no Melanoma

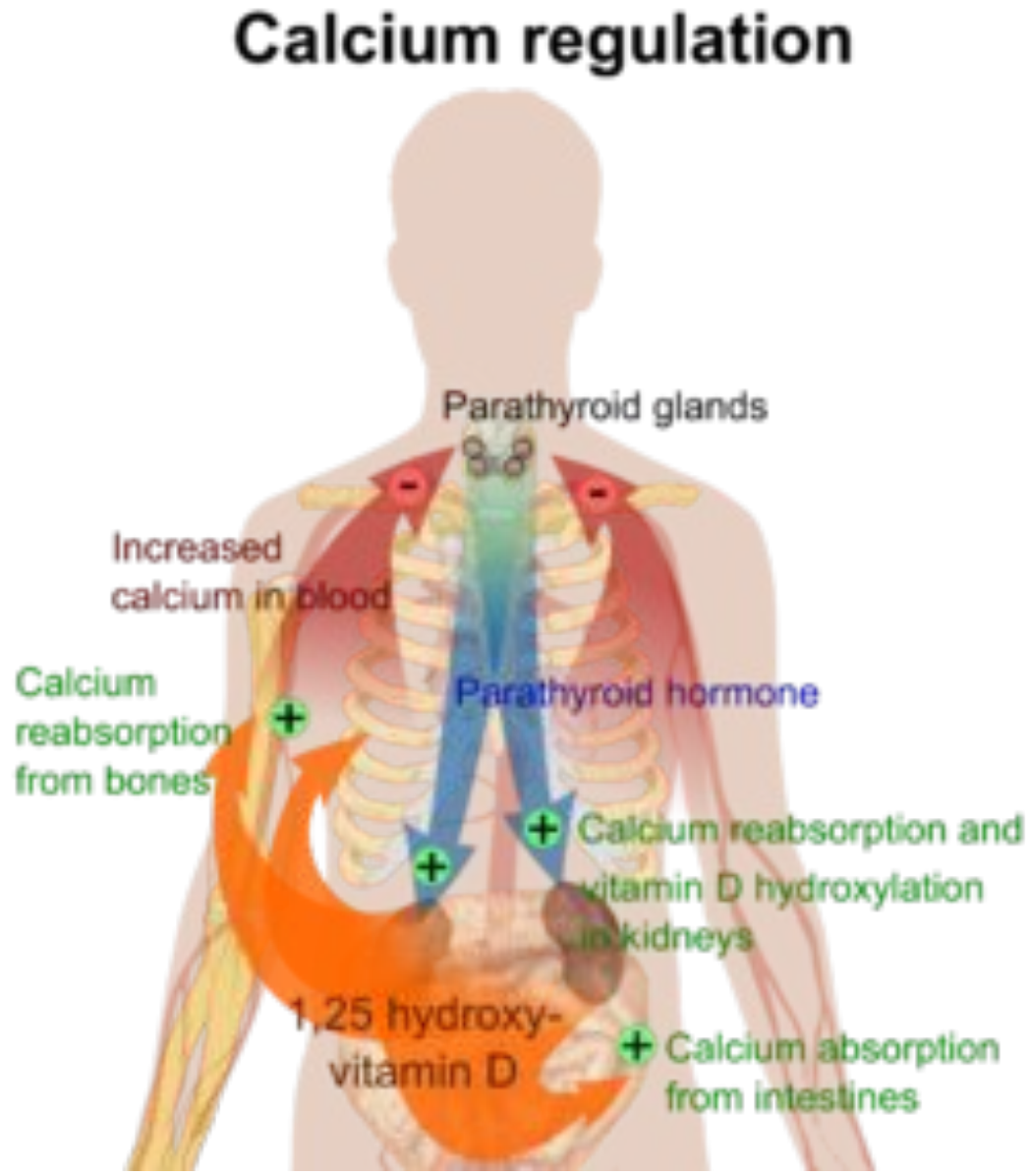
# Cause della diversità del colore della pelle

## 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.



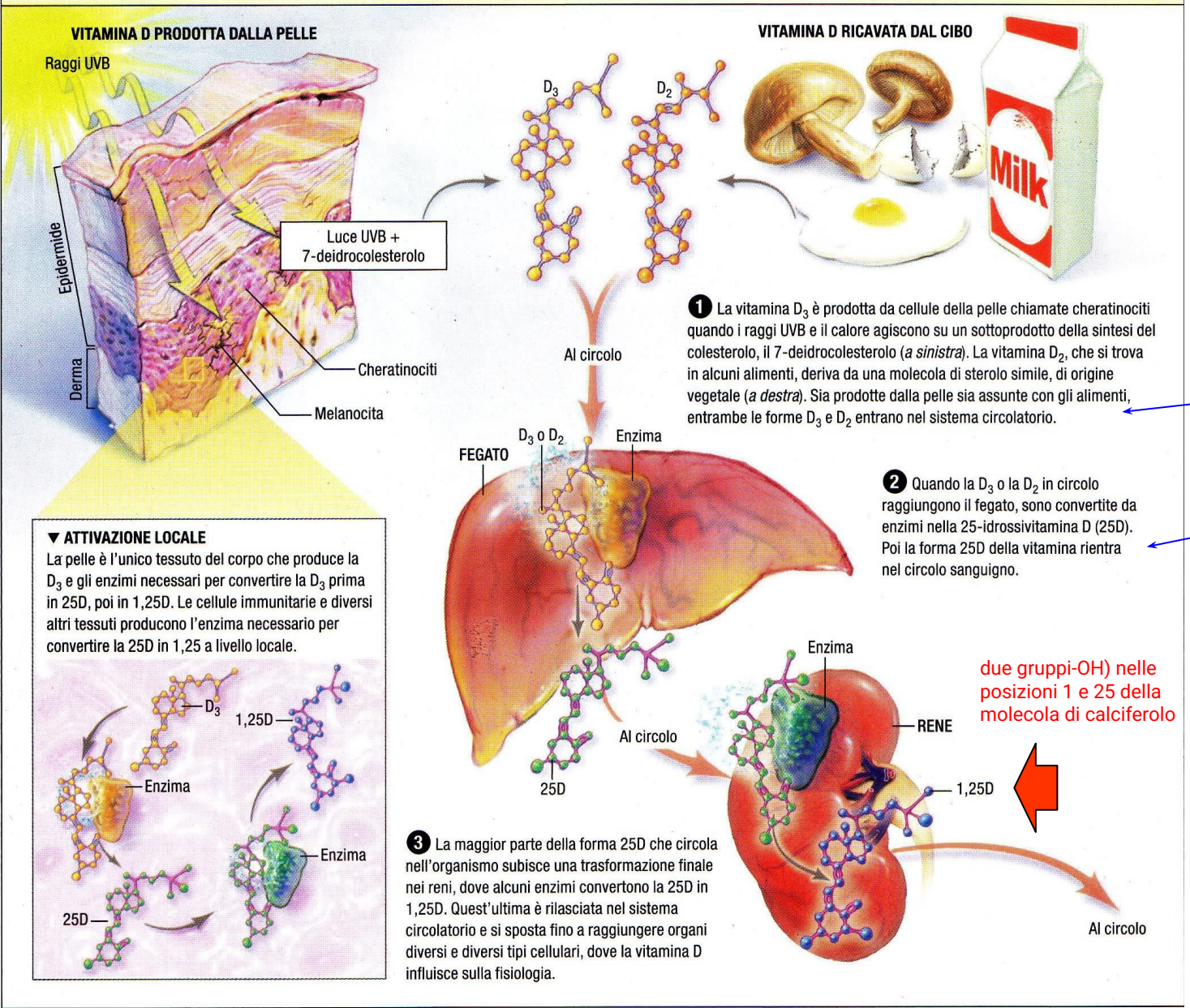

North or south of about 46°, levels of UVB are insufficient to initiate cutaneous production of previtamin D3 for much of the year




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.




due gruppi-OH) nelle posizioni 1 e 25 della molecola di calciferolo

$D_3$ 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

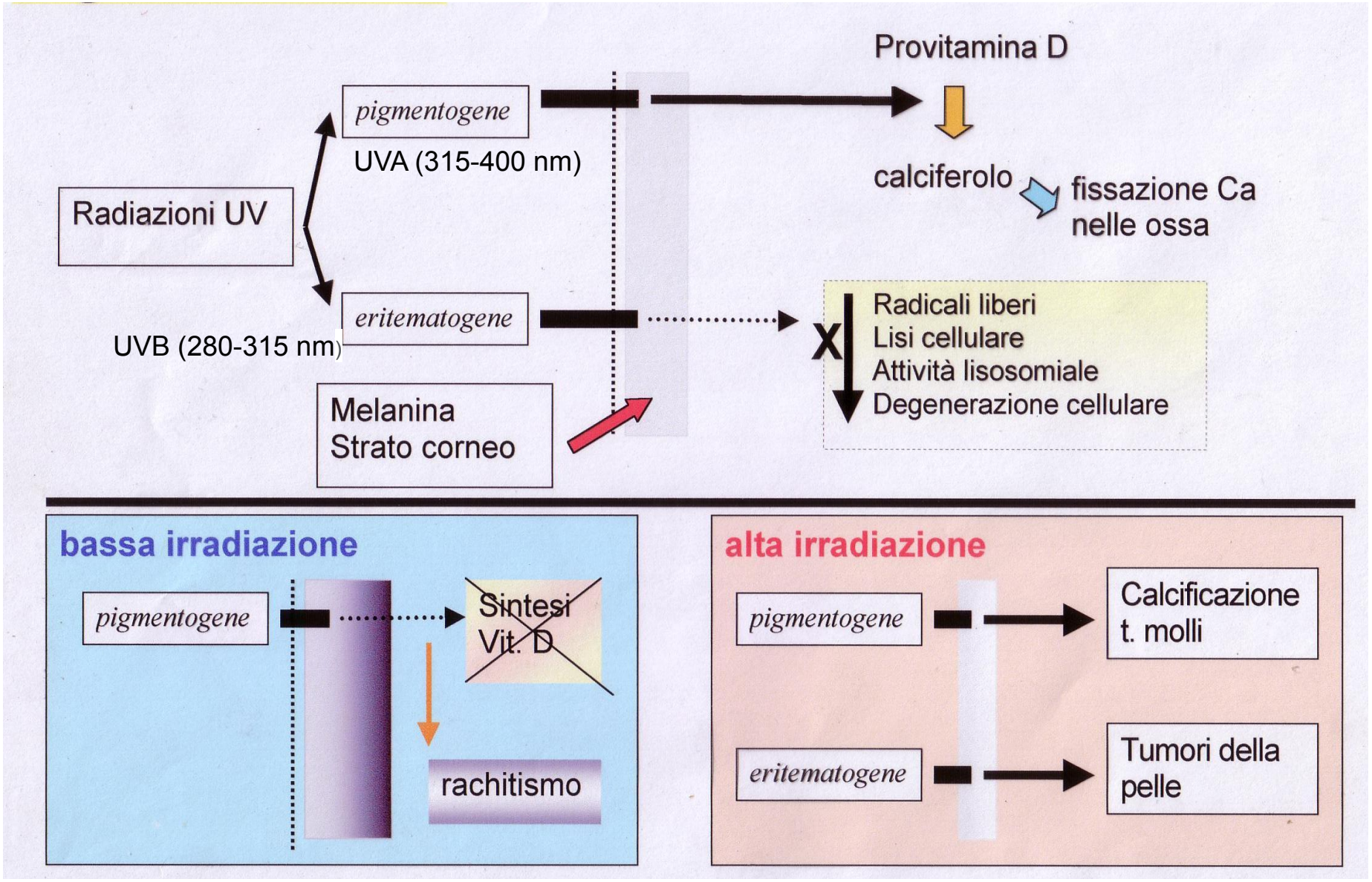
30-60 ng INTERVALLO PREFERIBILE

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

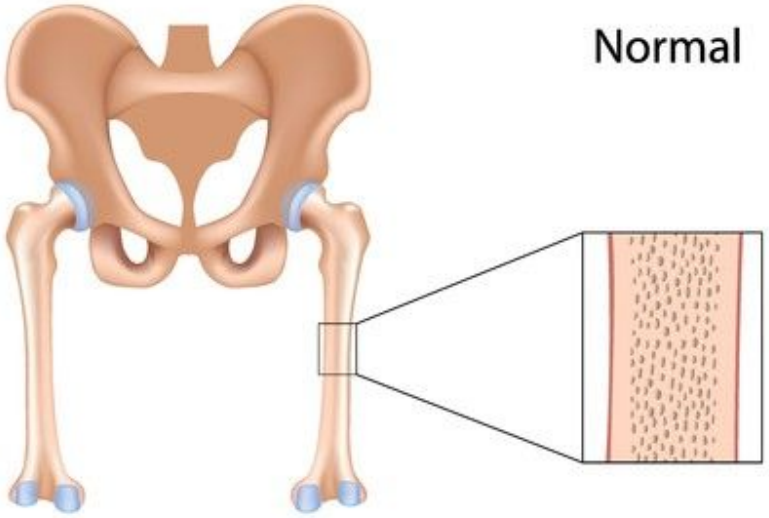
Nina G. Jablonski[1] and George Chaplin

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

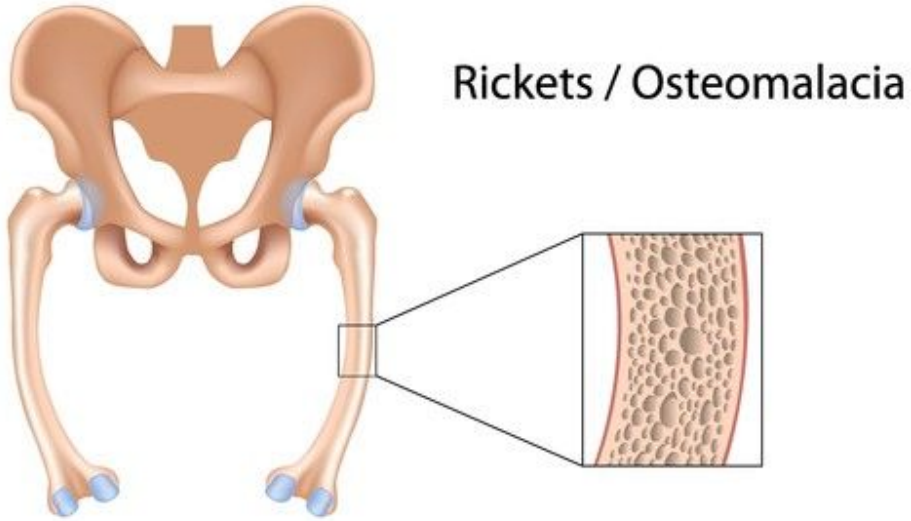
8962–8968 | PNAS | May 11, 2010 | vol. 107 | suppl. 2

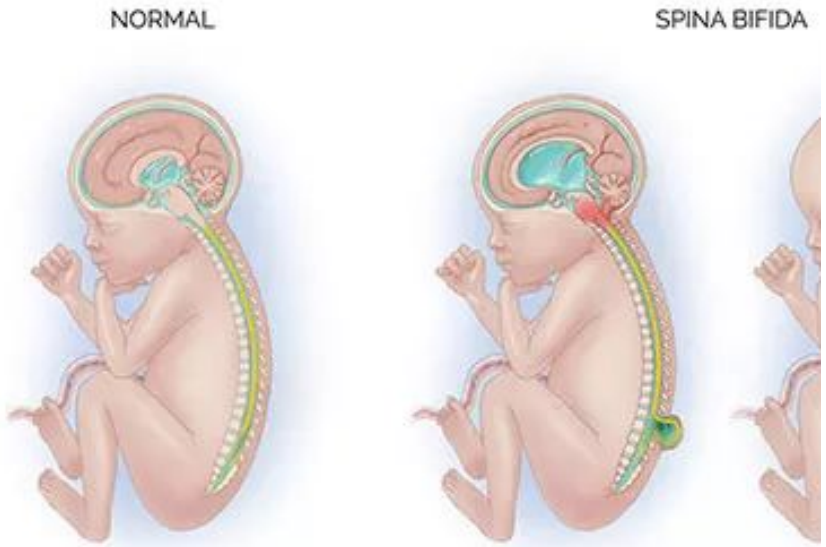
**Table 1. Summary of the effects of UVA and UVB on human body and the selective mechanisms involved in the evolution of pigmentation. The estimated strength of natural selection operating to darken and lighten pigmentation is indicated by numbers of "+" and "–" signs, respectively. See text for references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

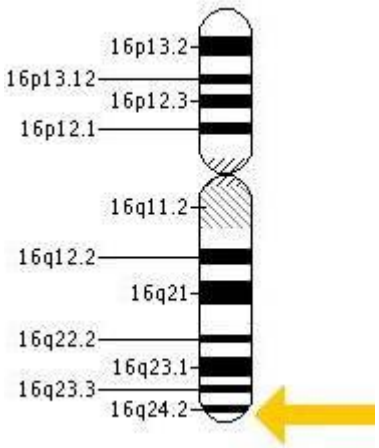
- G protein-coupled receptor which binds to a class of pituitary peptide hormones (melanocortins, e.g. melanocyte-stimulating hormones)

- 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

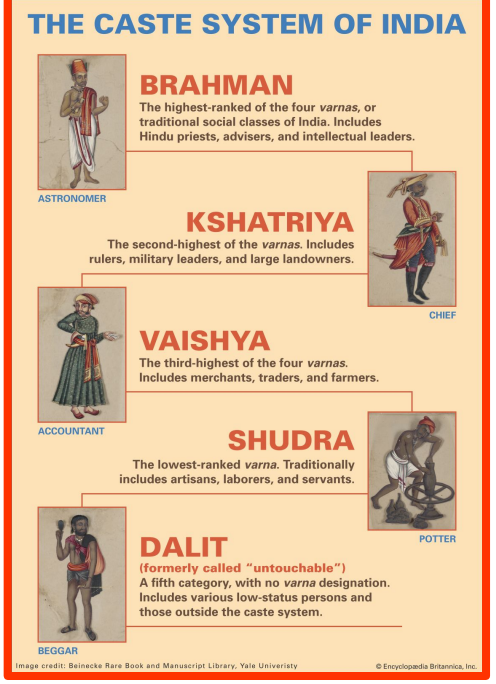
highly polymorphic in Northern European populations
not in Africa: selection against light skin

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

SLC24A5

**Epistasis**

**t**he 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.

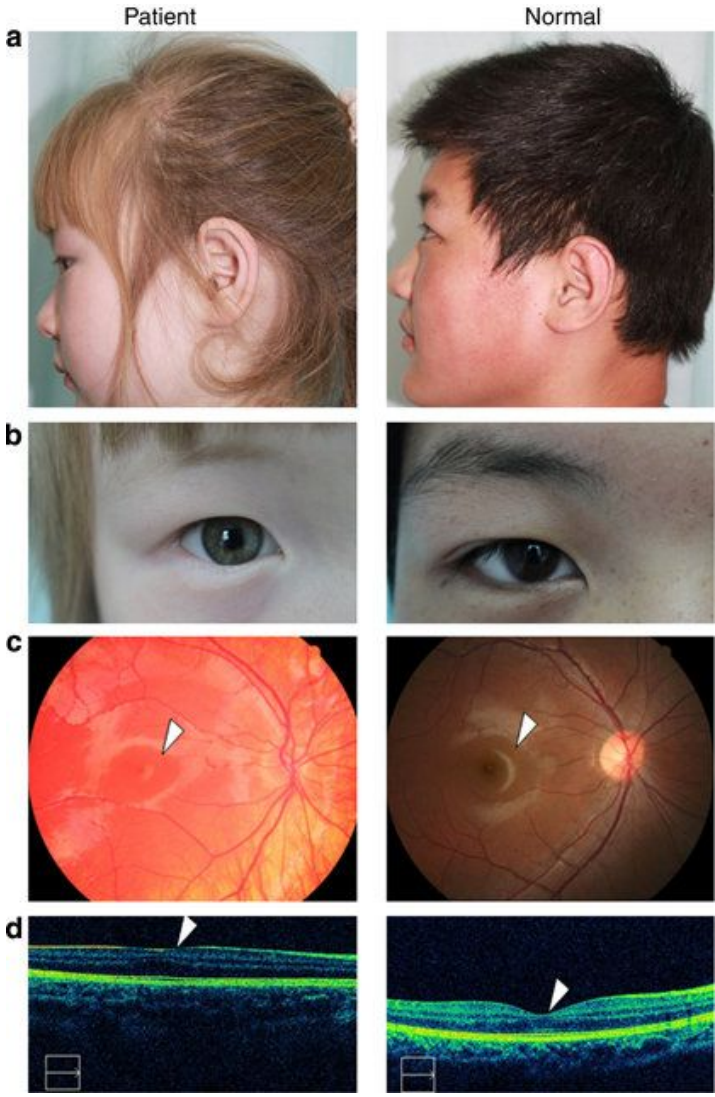
SNP rs1426654
polymorphism with the G and A alleles of the encoding alanine or threonine, respectively, at amino acid 111 in the third exon

**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?

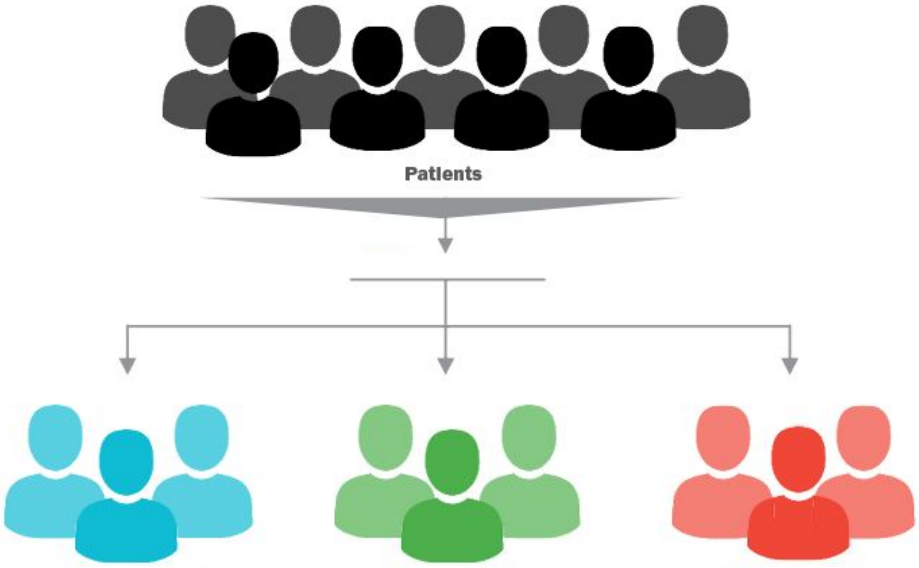
**The genes for light skin have been there since the beginning**. Chimp has light pigmentation, so skin color in the ancestors of modern humans could have been relatively light. It is likely that **when we lost the hair covering our bodies and moved from forests to the open savannah, we needed darker 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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$25*
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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).

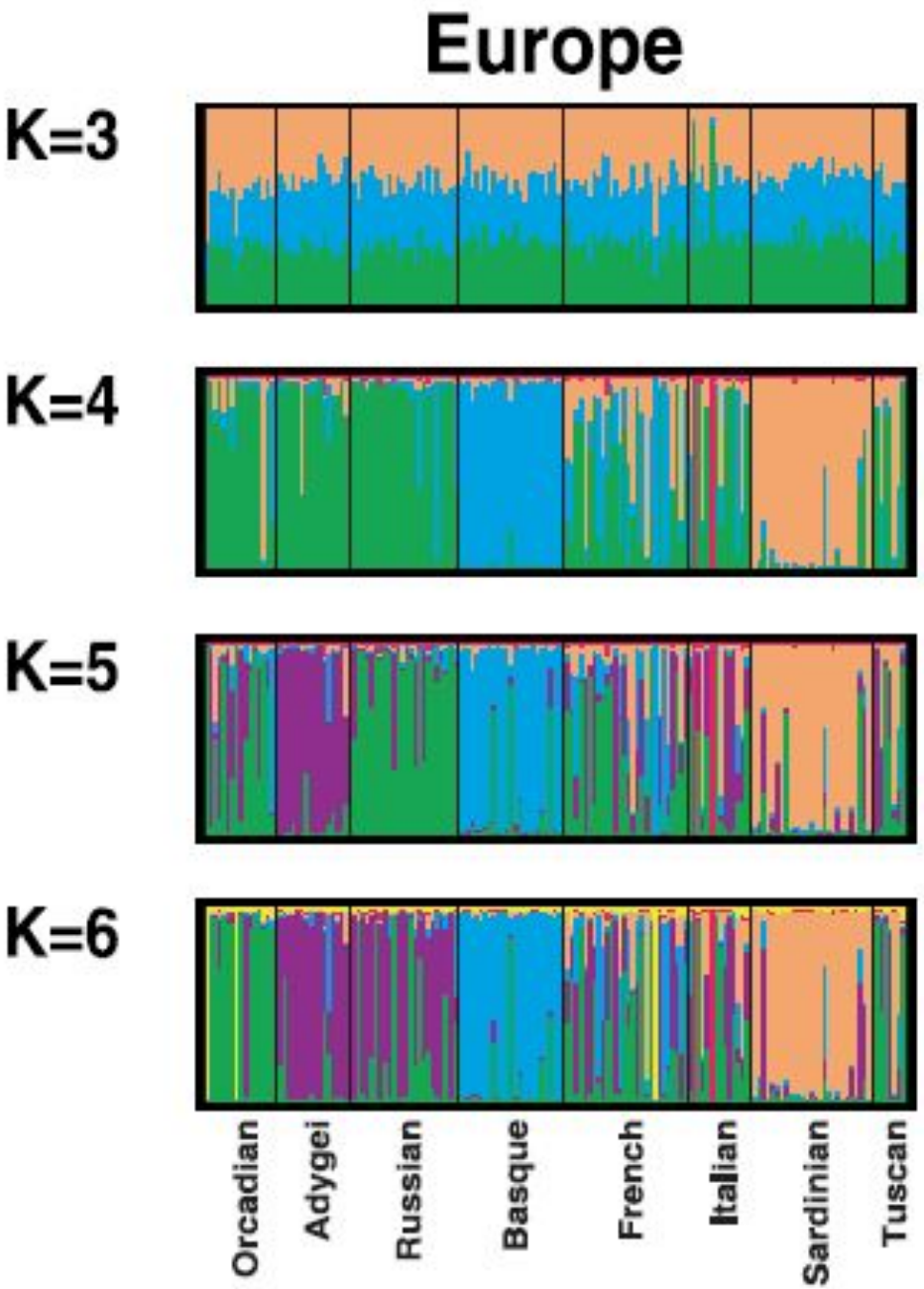
Analysis of the data produced four major genetic clusters, which showed near-perfect correspondence with the four self-reported race/ethnicity categories.

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.

# Genetic Structure of Human Populations

Noah A. Rosenberg,[1]* Jonathan K. Pritchard,[2] James L. Weber,[3] Howard M. Cann,[4] Kenneth K. Kidd,[5] Lev A. Zhivotovsky,[6] Marcus W. Feldman[7]

use of self-reported ancestry. In genetic case-control association studies, false positives can be obtained if disease risk is correlated with genetic ancestry (*24*, *26*). Basing analyses on self-reported ancestry reduces the proportion of false positives considerably (*25*). However, association studies are usually analyzed by significance testing, in which slight differences in genetic ancestry between cases and controls can produce statistically significant false-positive associations in large samples. Thus, errors incurred by using self-reported rather than genetic ancestry might cause serious problems in large studies that will be required for identifying susceptibility loci with small effects (*26*). Genetic clustering is also more appropriate for some types of population genetic studies, because unrecognized genetic structure can produce false positives in statistical tests for population growth or natural selection (*27*).



# 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.



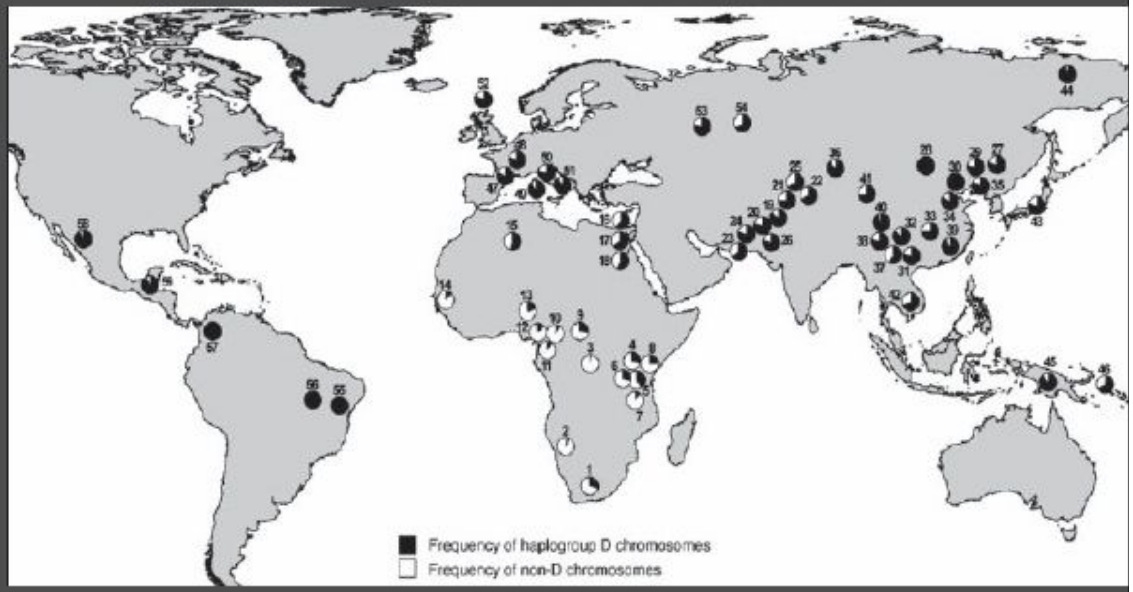
and 23 on the X chromosome in a heterogeneous group of individuals. Study participants were then assigned to four subclusters according to their microsatellite alleles, which roughly corresponded to four geographic areas: Western Eurasia, Sub-Saharan Africa, China, and New Guinea (Table 1).

# 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



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# Symptoms based approach

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

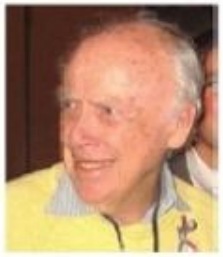
# Stratified medicine approach

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

*Treatment Decision* → Treatment B

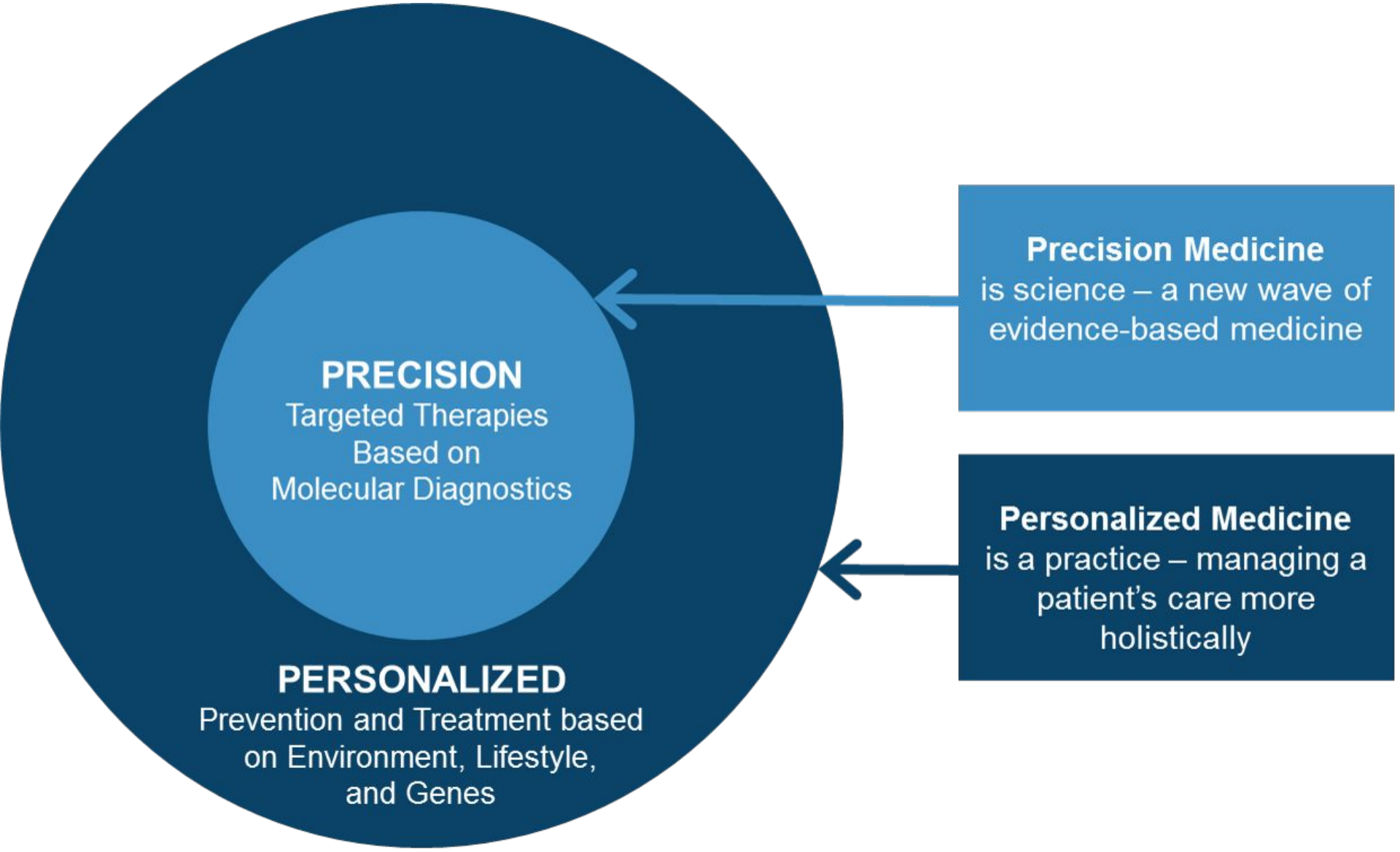
*Treatment Decision* → Treatment C

"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"

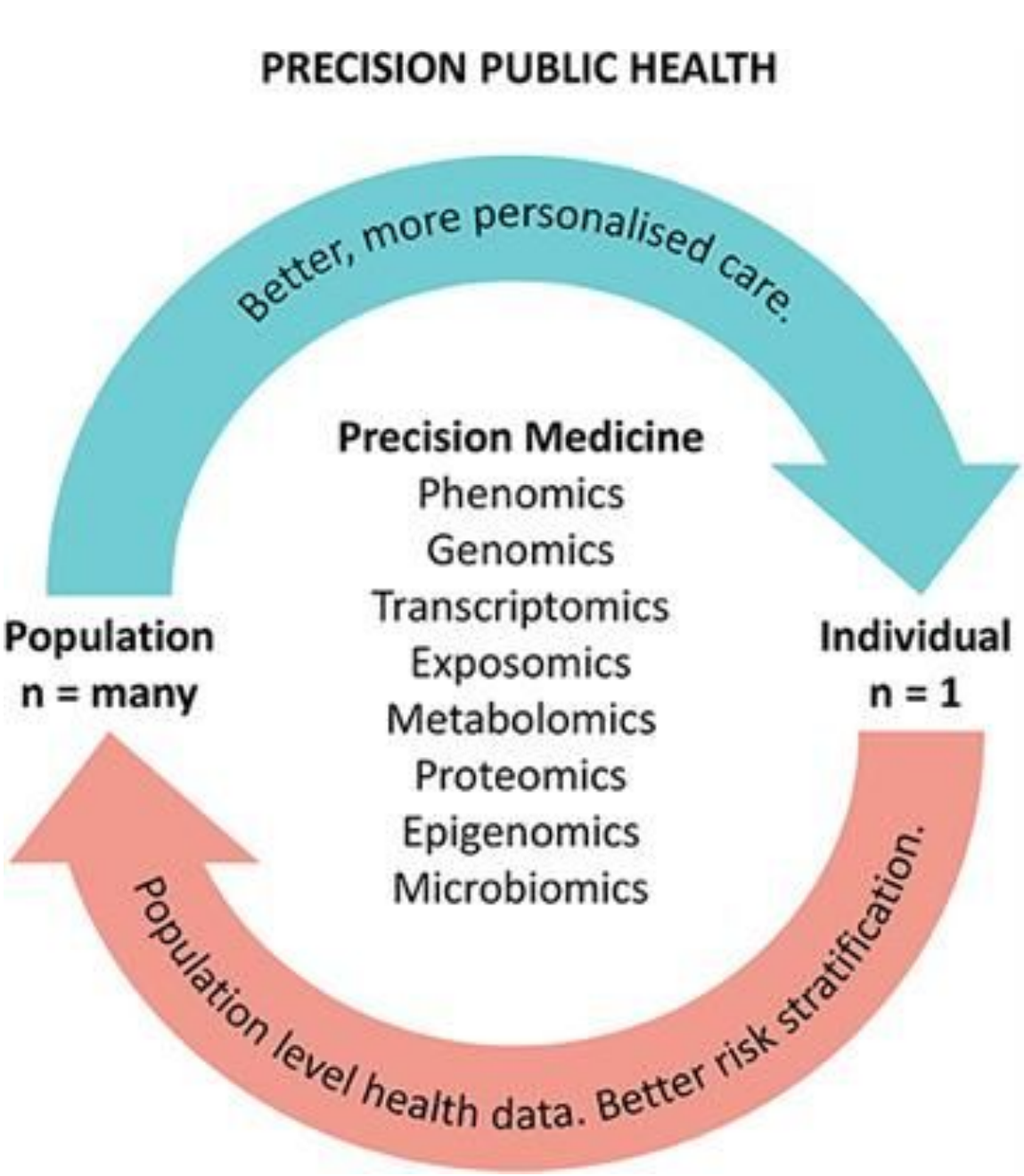


| Gene | Examples of substrates | James Watson | Craig Venter | Known effects |
|---|---|---|---|---|
| *CYP1A2* | Antipsychotics, caffeine, warfarin | **1F/*1F* | **1F/*1F* | **1F* influences the induction of *CYP1A2* activity |
| *CYP2C9* | Anti-inflammatory drugs, statins, warfarin, sulfonylurea (antidiabetic), 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

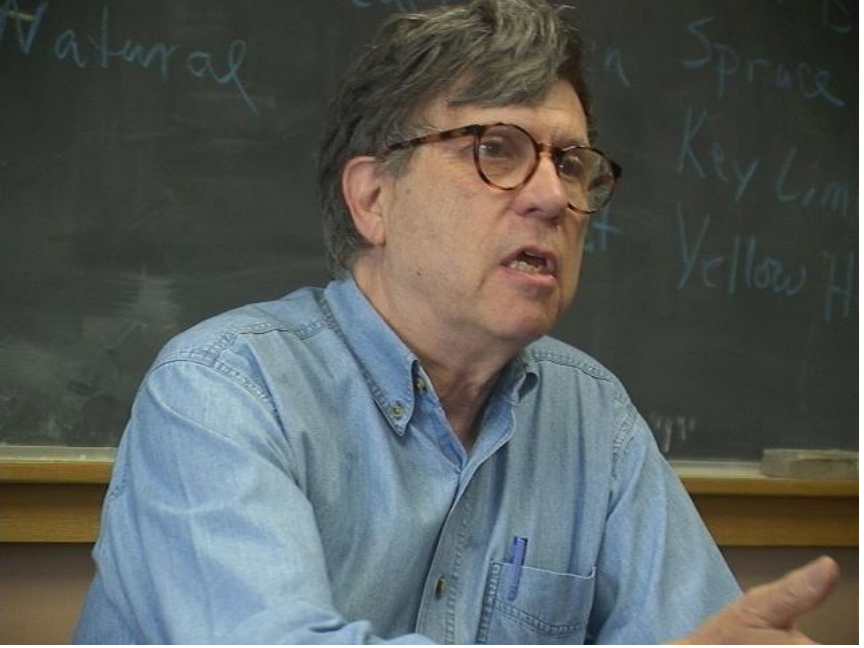

PRECISION
Targeted Therapies
Based on
Molecular Diagnostics
PERSONALIZED
Prevention and Treatment based
on Environment, Lifestyle,
and Genes
Precision Medicine
is science – a new wave of
evidence-based medicine
Personalized Medicine
is a practice – managing a
patient's care more
holistically

**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)

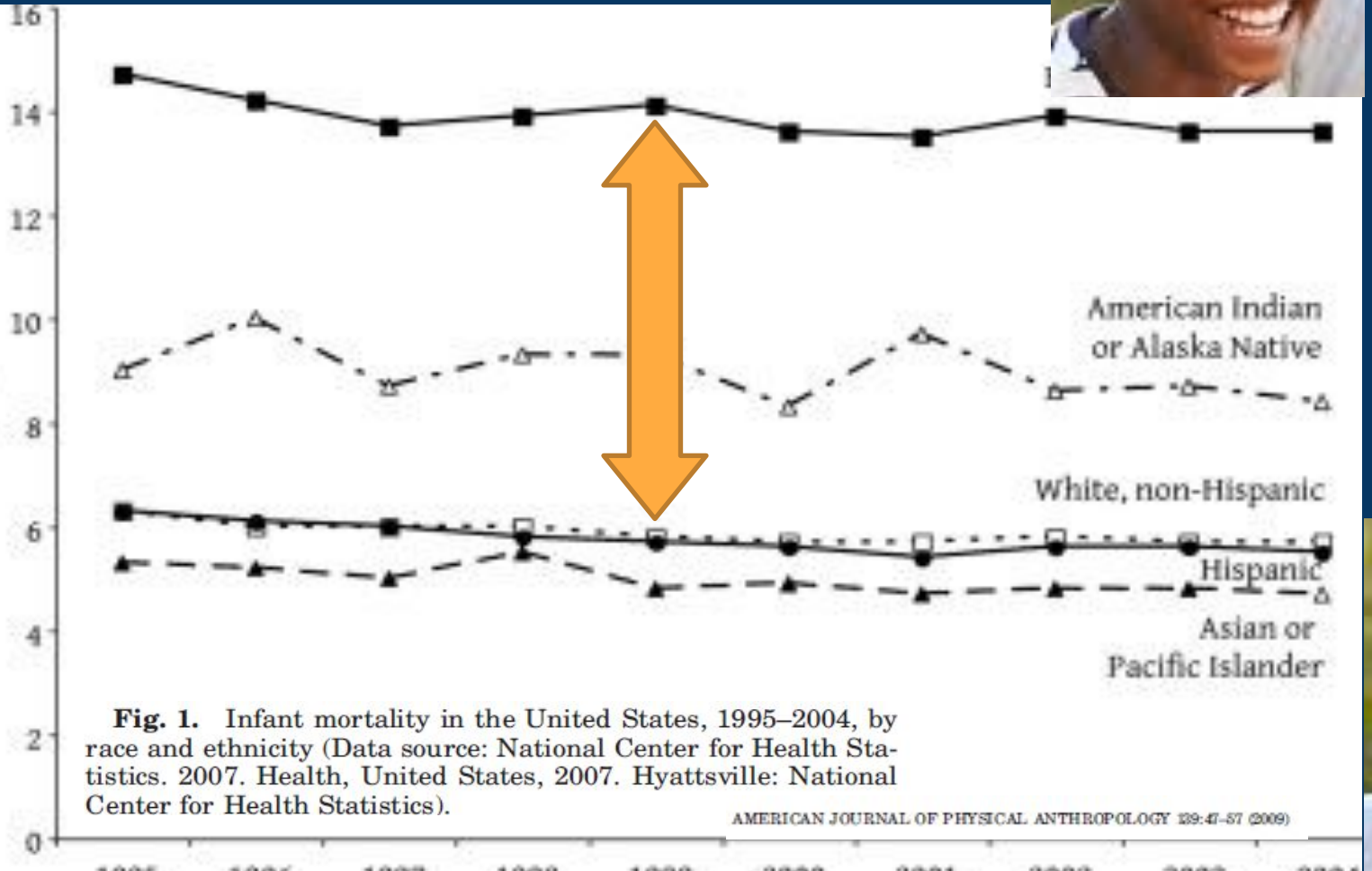
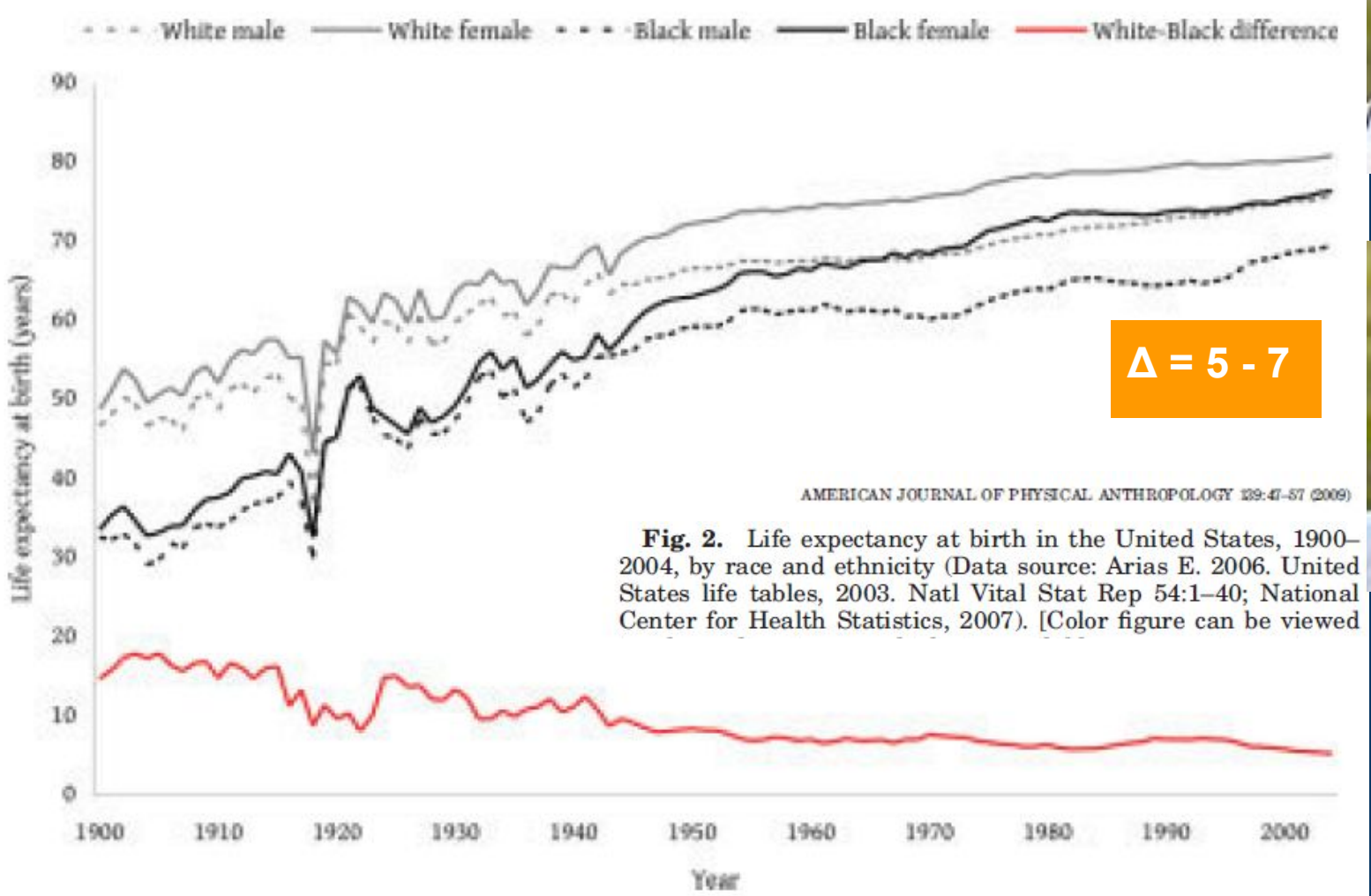



**Fig. 1.** Infant mortality in the United States, 1995–2004, by race and ethnicity (Data source: National Center for Health Statistics. 2007. Health, United States, 2007. Hyattsville: National Center for Health Statistics).

AMERICAN JOURNAL OF PHYSICAL ANTHROPOLOGY 139:47–57 (2009)

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




AMERICAN JOURNAL OF PHYSICAL ANTHROPOLOGY 139:47–57 (2009)

**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

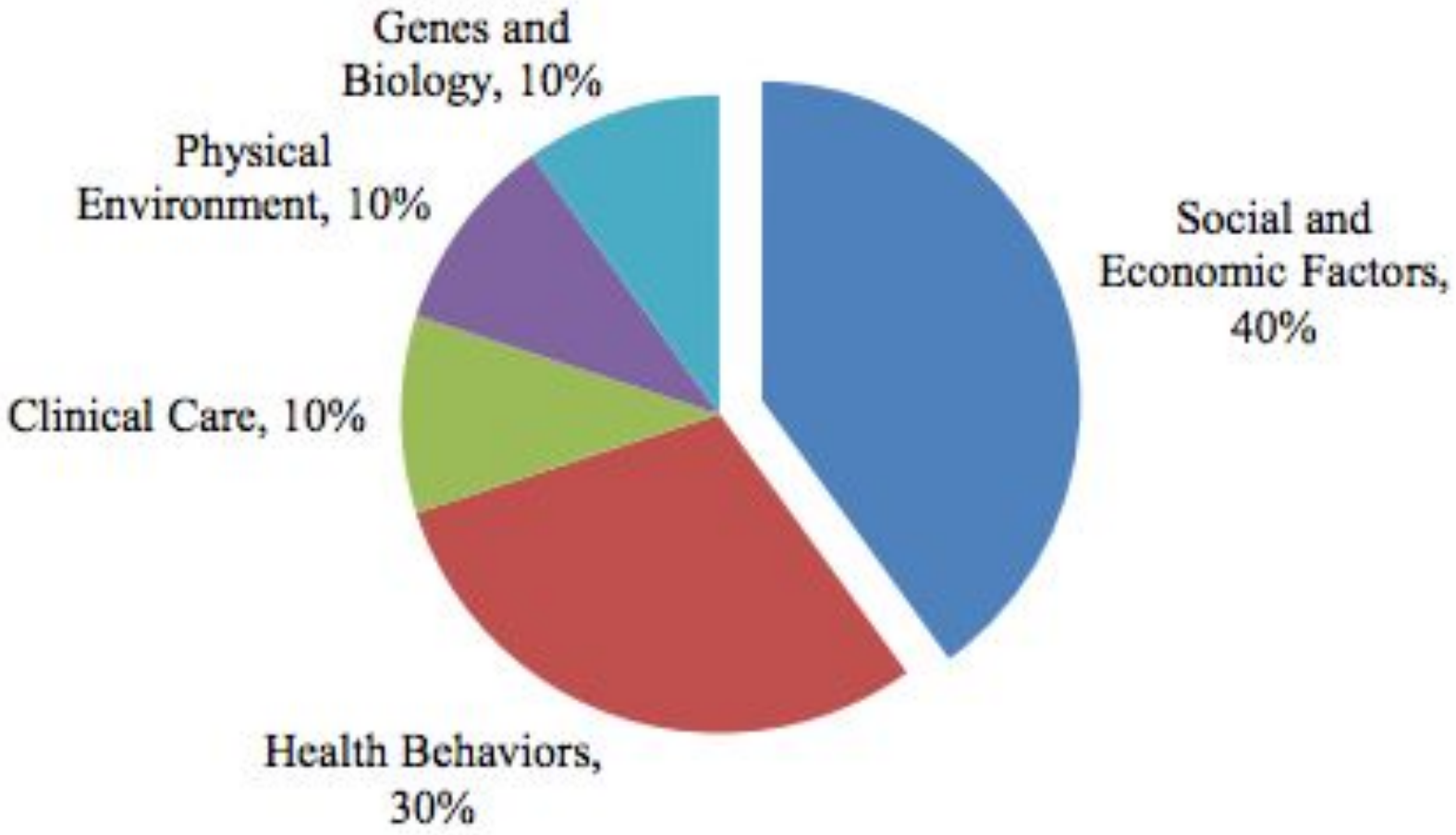
il tasso di mortalità corretto per l'età è superiore di oltre il 30% negli afroamericani

# … 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