Ecological dynamics for the study of the genetics of aging and age-related diseases

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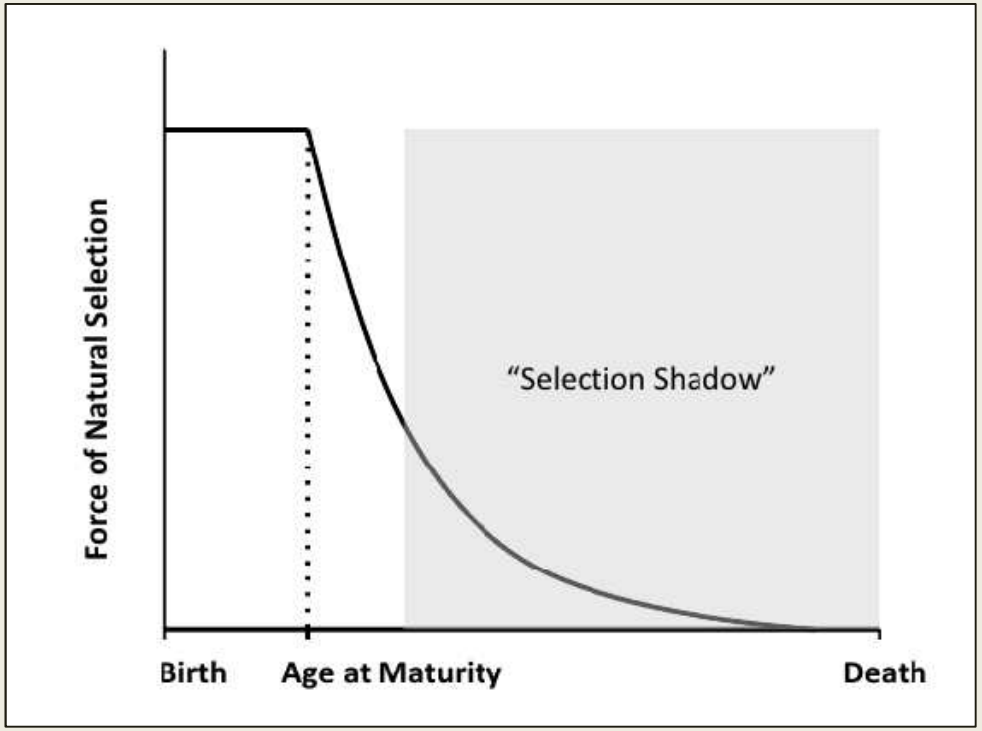
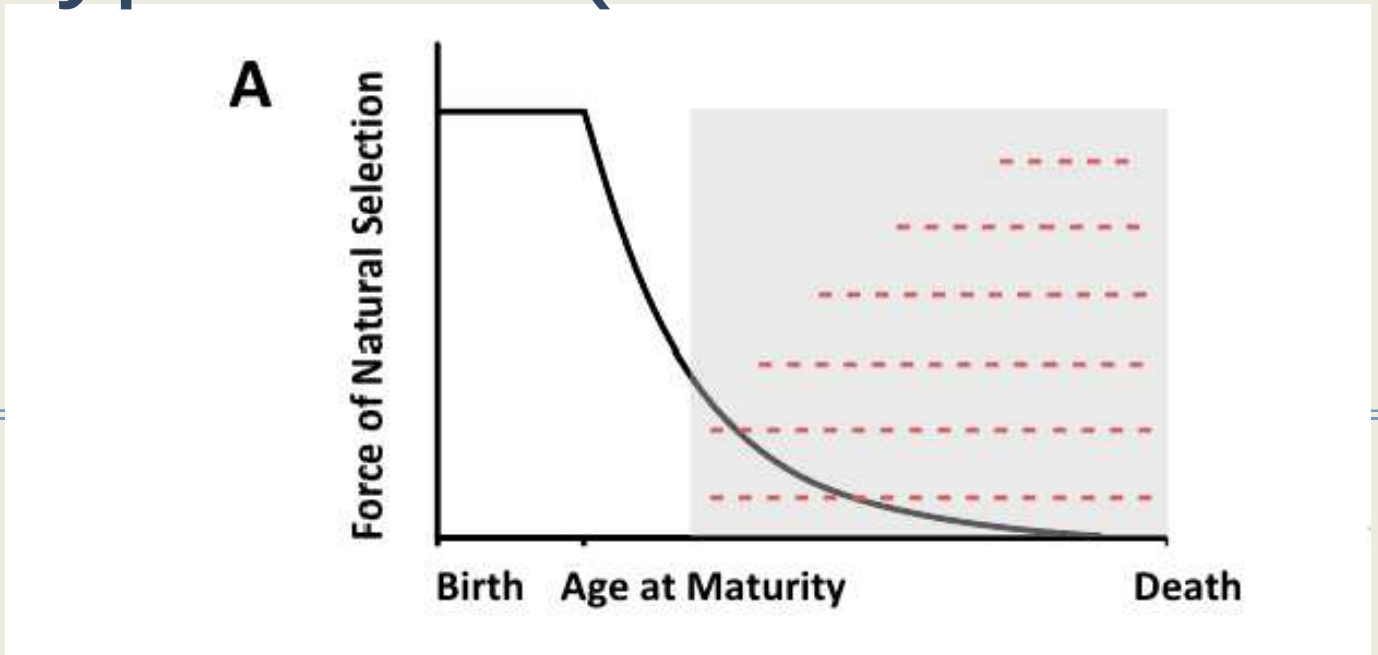
EVOLUTIONARY THEORIES OF AGEING

Medawar (1946)



The force or strength of natural selection, a measure of how strongly selection acts on survival and/or reproduction, **declines as a function of age, a major theoretical insight developed by J.B.S. Haldane and Peter B. Medawar that was later mathematically formalized by William D. Hamilton**. In the shaded area (the "selection shadow") **selection cannot "see" deleterious mutations whose effects are confined to late ages:** a harmful mutation that has a negative effect that is restricted to late life will likely already have been passed on to the offspring of the individuals bearing it, and selection will thus be **inefficient at eliminating such a mutation from the population**. The concept of the declining force of selection is the fundamental basis for the evolutionary theories of aging .

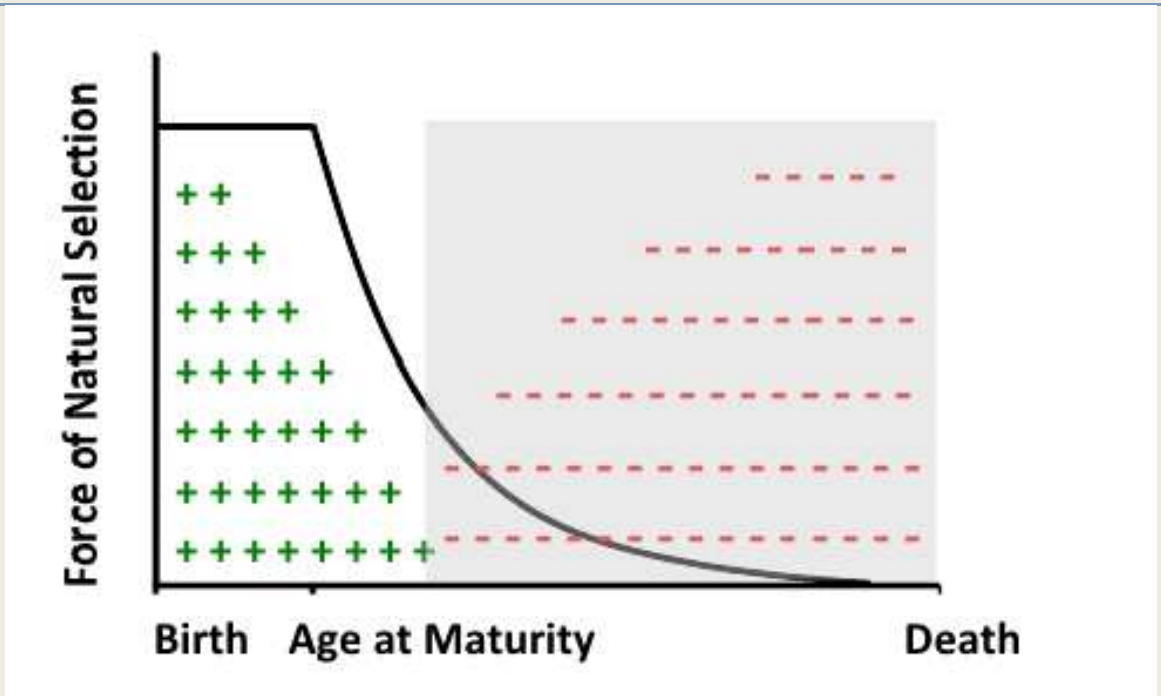
The Mutation accumulation hypothesis (Medawar, 1946)



Mutation Accumulation. Medawar realized that, if the force of selection declines with age, mutations or alleles that are **neutral** (i.e., have no effect) early in life, when selection is strong, but **deleterious effects late in life**, when selection is weak (shaded area) could accumulate in the population. Such late-life deleterious genetic variants can lead to the evolution of aging, an idea called the mutation accumulation (MA) theory of aging.

More info:
https://www.nature.com/scitable/knowledge/library/the-evolution-of-aging-23651151

Antagonistic pleiotropy (Williams, 1957)

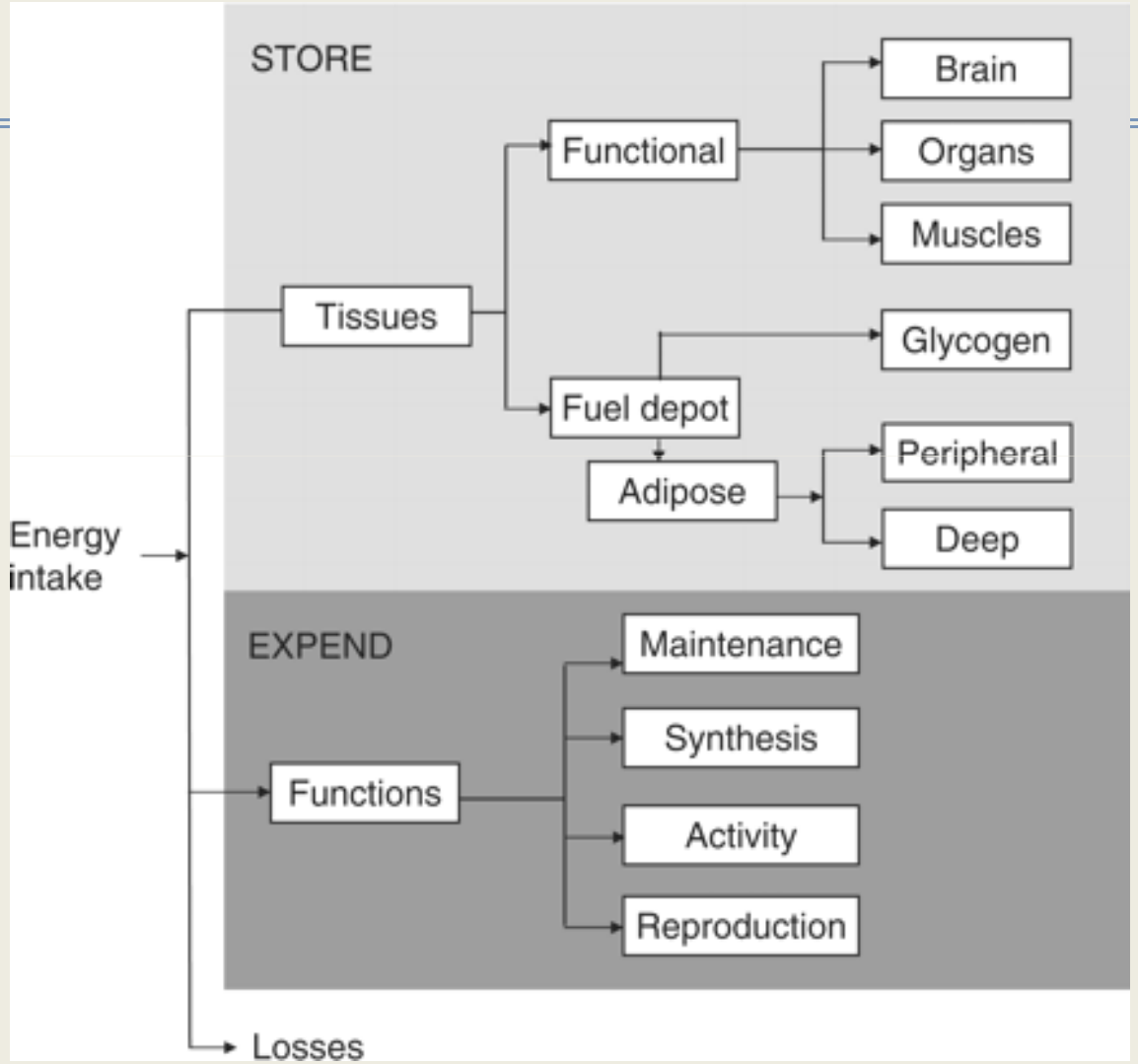


Williams developed Medawar's idea further by realizing that strong selection at early ages might favor mutations or alleles with beneficial effects on survival and reproduction, even if these same mutations or alleles exhibit pleiotropic deleterious effects at advanced ages

Disposable soma (Kirkwood, 1977)

- A limited amount of energy that has to be divided between **reproductive activities** and the **maintenance of the non-reproductive aspects of the organism**.
- Somatic cells are maintained only to ensure continued reproductive success, following reproduction the soma is disposable
- The disposable soma theory of aging acts on the premise that there is a *tradeoff in resource allocation between somatic maintenance and reproductive investment*.

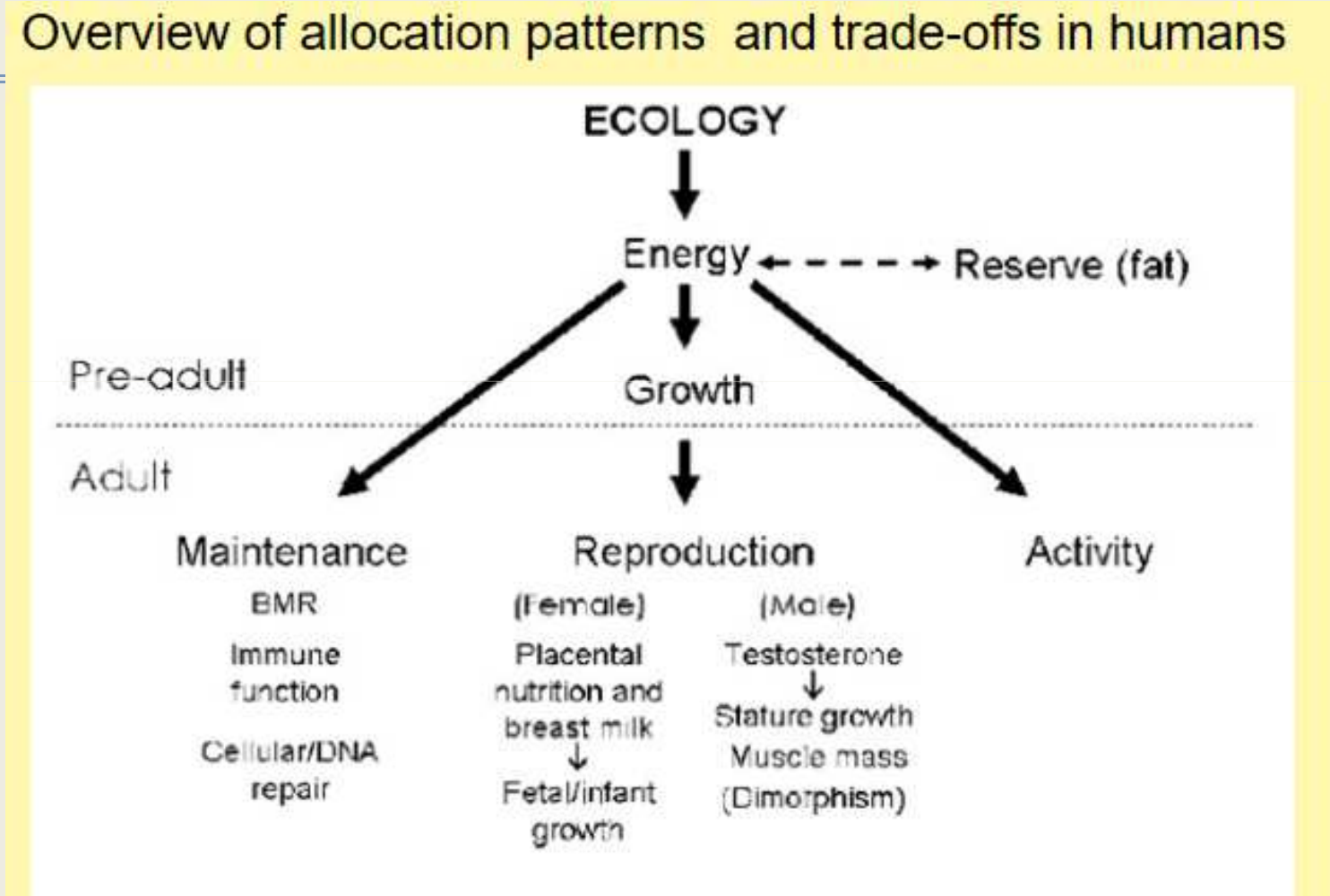
ENERGY ALLOCATION



The relative prioritization of these different ends varies as a function of numerous factors such as age, gender, pubertal maturation, reproductive status and health.

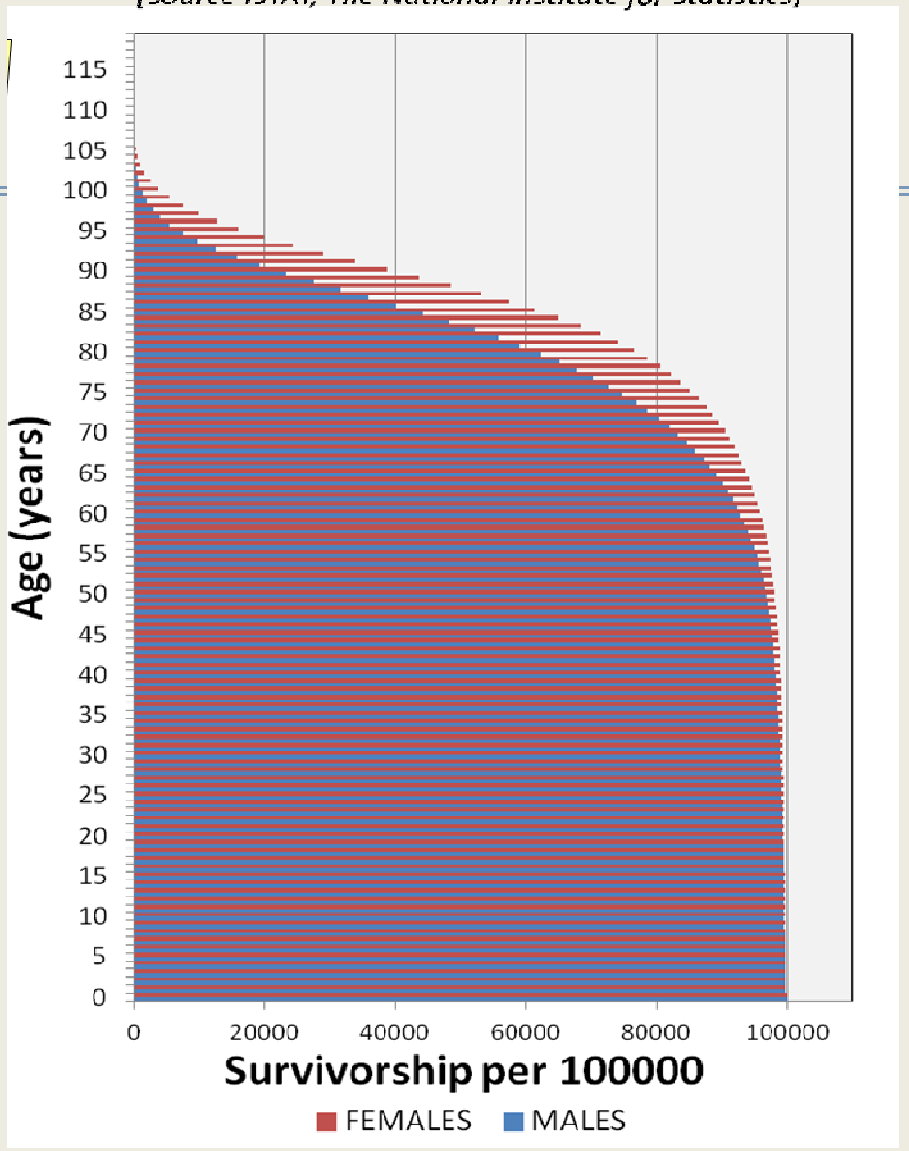
Wells 2009 "Ethnic variability in adiposity and cardiovascular risk: the variable disease selection hypothesis" Int J Epidemiol.

ENERGY ALLOCATION



LONGEVITY IN MALES AND FEMALES

Longevity in male and female



Sex hormones: the example of Korean population of eunuchs

Current Biology

Volume 22, Issue 18, 25 September 2012, Pages R792-R793

Correspondence

The lifespan of Korean eunuchs

Kyung-Jin Min [1, *], Cheol-Koo Lee [2, *], Han-Nam Park [3]

Show more

https://doi.org/10.1016/j.cub.2012.06.036

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"The average lifespan of eunuchs was 70.0 ± 1.76 years, which was 14.4–19.1 years longer than the lifespan of non-castrated men of similar socio-economic status. Our study supports the idea that male sex hormones decrease the lifespan of men"

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ScienceDirect

Ageing Research Reviews 6 (2007) 28–45

ageing research reviews

www.elsevier.com/locate/arr

Review

Hormonal regulation of longevity in mammals

Holly M. Brown-Borg *

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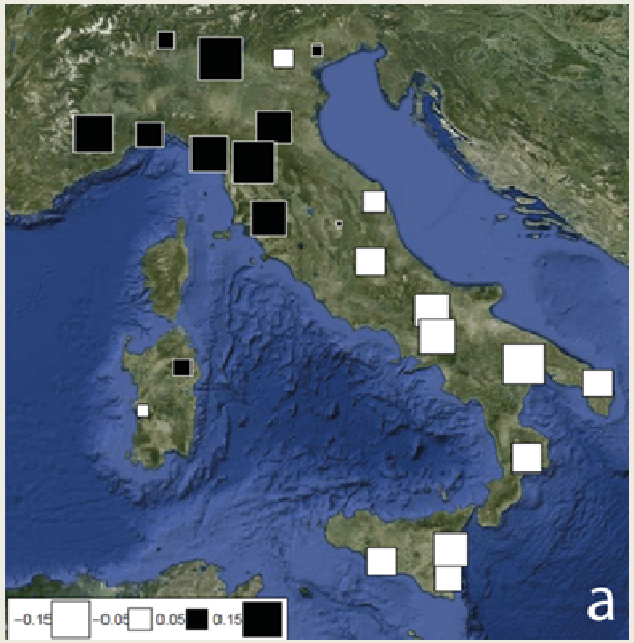
- In male, there is a trade-off between **immune investment** and traits that improve competitive success, which has driven genetic variation in genes involved in t**estosterone** levels during human evolution. Since immune responses are energy demanding processes, *testosterone plays a major role in male to increase muscle growth but at the same time reduce immune response* (testosterone is considered an immunosuppressant).

Culture: grandmother hypothesis

- In the difference between male and female the cultural processes need also to be considered: in certain societies some genes that slow down aging rate may be selected because of the advantage they can confers for fitness and survival of the offspring.

Male:female ratio of centenarians in Italy – Role of Genetics?

Passarino et al. 2002



Boattini et al., 2015 - Y chromosome

LONGEVITY RUNS IN FAMILIES

OFFSPRING

- Centenarians offspring are characterized by a better health status when compared with age-matched controls born from parents who died before reaching the expected lifespan for their cohort
- Not only genes but also culture
- DNA methylation age (epigenetic clock)

Impact Journals: AGING Open-Access Impact Journal on Aging

Aging (Albany NY). 2016 Mar; 8(3): 510–519.
Published online 2016 Mar 12. doi: 10.18632/aging.100912
PMCID: PMC4833142
PMID: 26979133

Centenarians' offspring as a model of healthy aging: a reappraisal of the data on Italian subjects and a comprehensive overview

Laura Bucci,[#1] Rita Ostan,[#1] Elisa Cevenini,[1] Elisa Pini,[1] Maria Scurti,[1] Giovanni Vitale,[2,3] Daniela Mari,[2,3,4] Calogero Caruso,[5] Paolo Sansoni,[6] Flaminia Fanelli,[7] Renato Pasquali,[7] Paola Cuercsi,[8] Claudio Franceschi,[1,§] and Daniela Monti[9,§]

Impact Journals: AGING Open-Access Impact Journal on Aging

Aging (Albany NY). 2015 Dec; 7(12): 1159–1170.
Published online 2015 Dec 15. doi: 10.18632/aging.100861
PMCID: PMC4712339
PMID: 26678252

Decreased epigenetic age of PBMCs from Italian semi-supercentenarians and their offspring

Steve Horvath,[1,2,*] Chiara Pirazzini,[3,4,*] Maria Giulia Bacalini,[3,4,5] Davide Gentilini,[6] Anna Maria Di Blasio,[6] Massimo Delledonne,[5,7] Daniela Mari,[8,9] Beatrice Arosio,[8,9] Daniela Monti,[10] Giuseppe Passarino,[11] Francesco De Rango,[11] Patrizia D'Aquila,[11] Cristina Giuliani,[12] Elena Marasco,[3,4] Sebastiano Collino,[13] Patrick Descombes,[14] Paolo Garagnani,[3,4,15,§] and Claudio Franceschi[3,4,16,17,§]

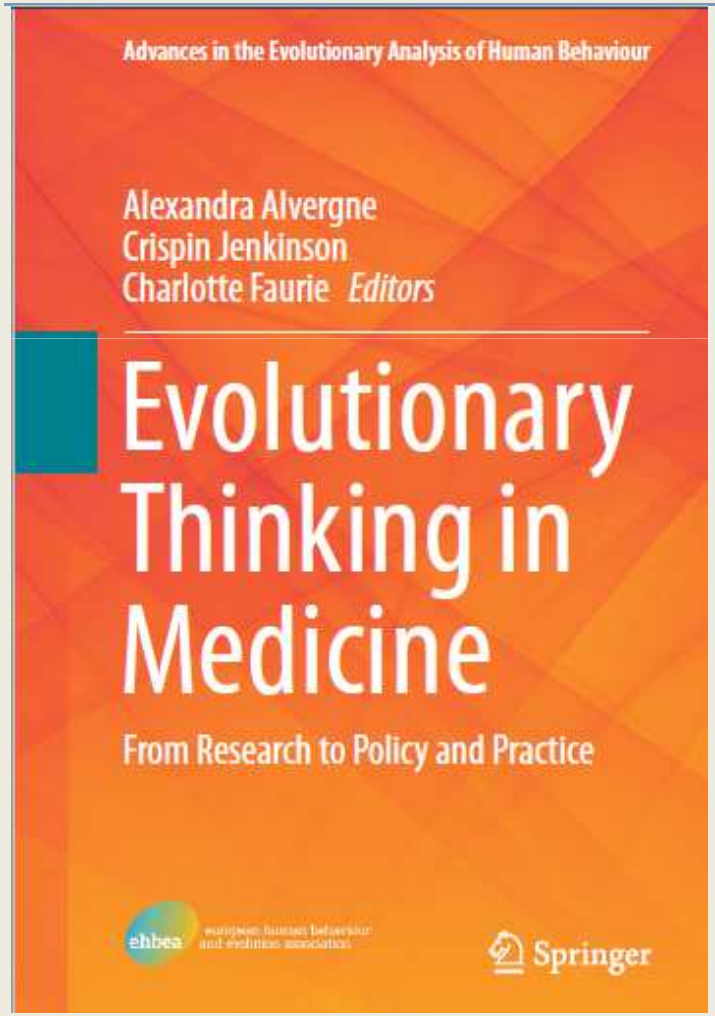
LONGEVITY RUNS IN FAMILIES

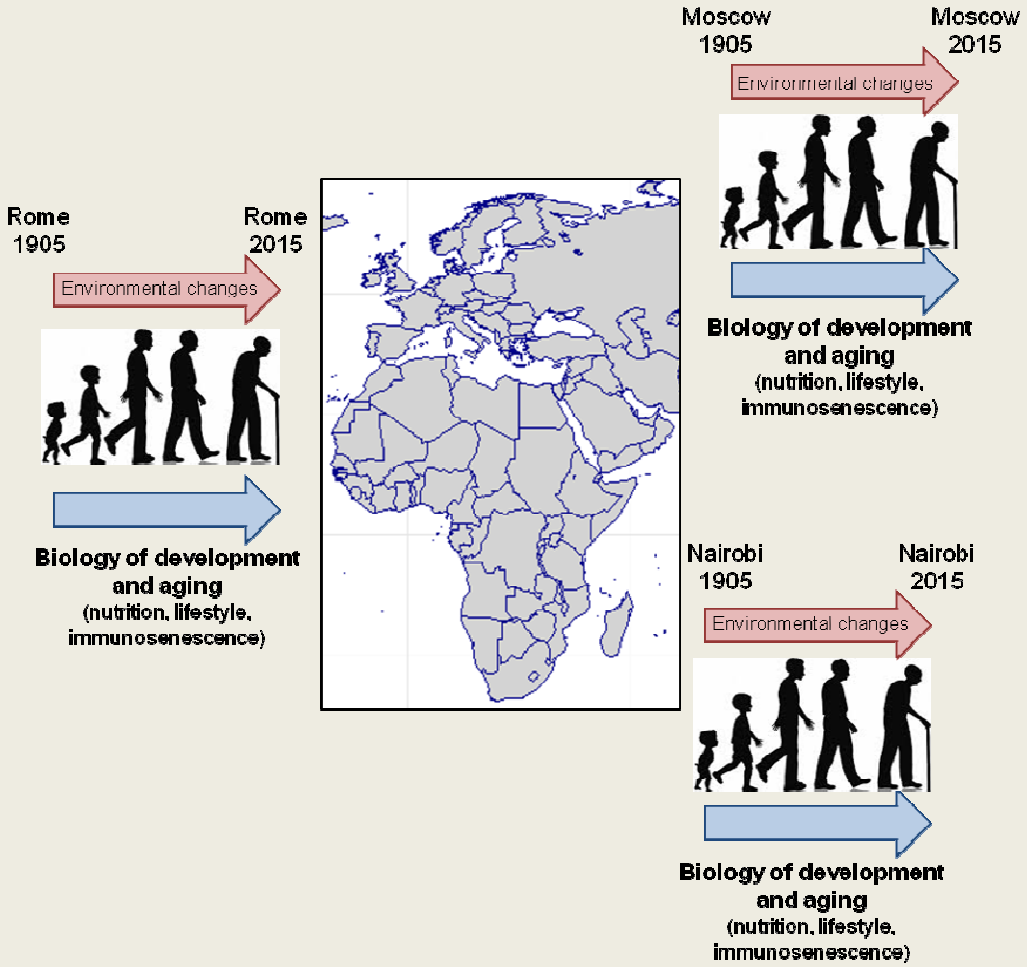
SPOUSES

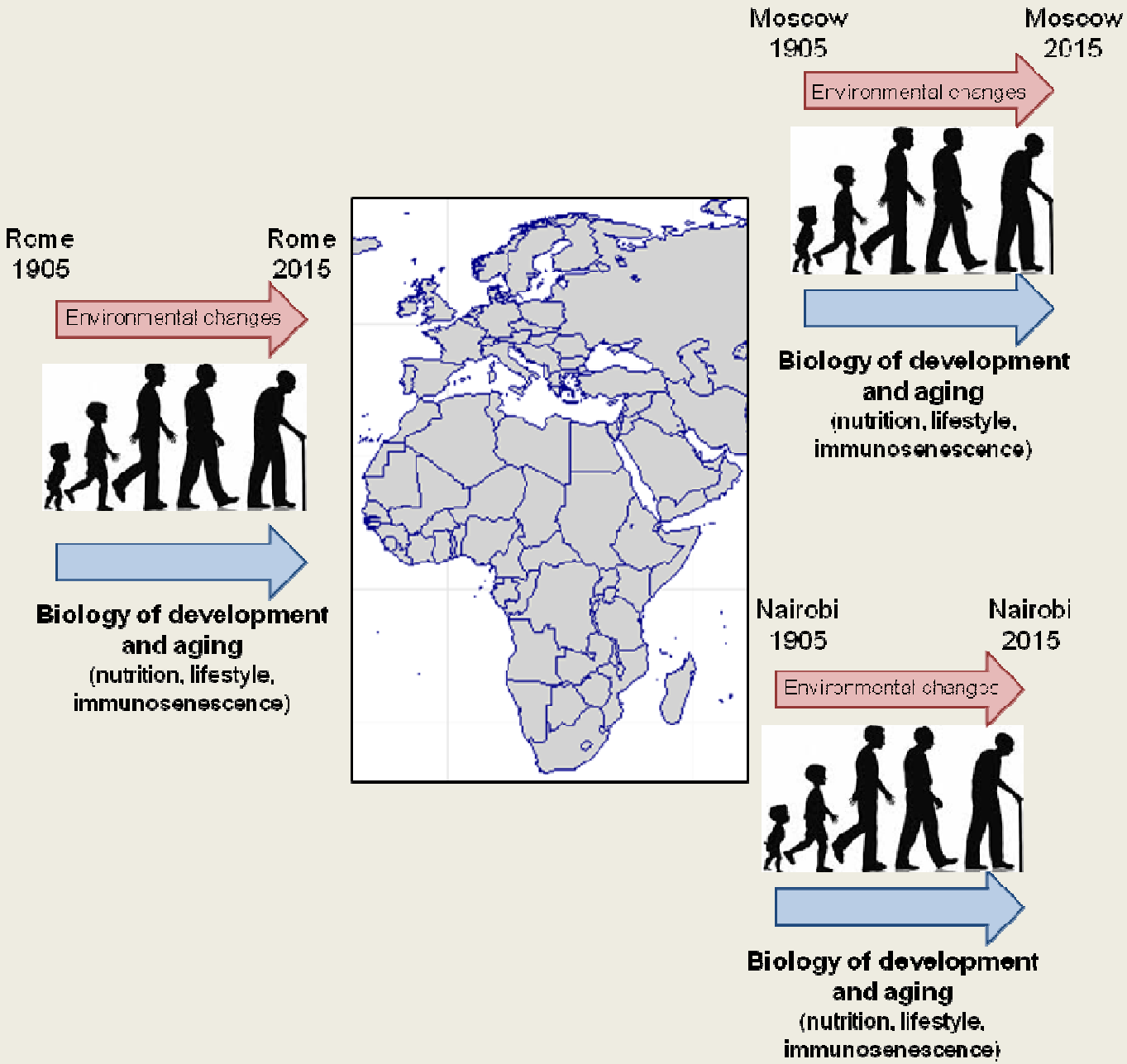
- DUTCH: The first found that spouses of long-lived partner, even sharing most of their adult life with their partner, did not present any advantage in term of survival, suggesting that the effect observed were mainly linked to genetic factors (Schoenmaker "**Evidence of genetic enrichment for exceptional survival using a family approach: the Leiden Longevity Study**" 2006)

- CALABRIA: This is not the case of a population from South of Italy (Calabria) characterized by a totally different social scenario. Spouses of long-lived siblings also live longer than members of the corresponding birth cohort (Montesanto "**The genetic component of human longevity: analysis of the survival advantage of parents and siblings of Italian nonagenarians**" 2011)

LONGEVITY IS POPULATION SPECIFIC






Moscow
1905
Moscow
2015
Environmental changes
Biology of development
and aging
(nutrition, lifestyle,
immunosenescence)
Rome
1905
Rome
2015
Environmental changes
Biology of development
and aging
(nutrition, lifestyle,
immunosenescence)
Nairobi
1905
Nairobi
2015
Environmental changes
Biology of development
and aging
(nutrition, lifestyle,
immunosenescence)

Longevity (but also inflammaging) is
a population specific process,
because the evolutionary history
of each population may have
shaped the ability to
cope with specific stressors
(e.g. infectious agents and food)
typical of the context
and of the specific environment.

Who are the ancestors of modern humans?

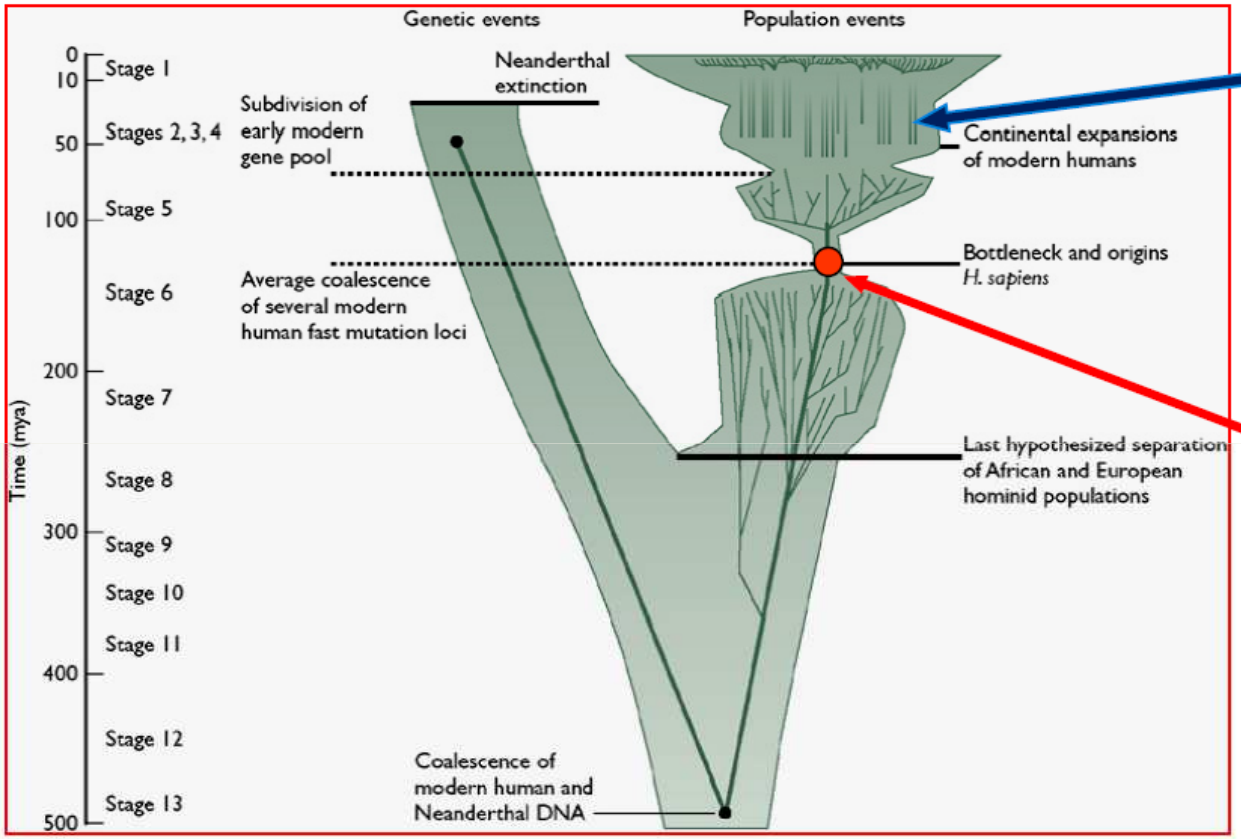
Most anthropologists think that H. sapiens **first evolved in sub-Saharan Africa about 200,000 years ago** (see also paper Henn 2011, PNAS http://www.pnas.org/content/early/2011/03/01/1017511108)

and began **migrating out of Africa between 70,000 and 50,000 years ago**. Many researchers are beginning to suspect that moderns left Africa in two or more waves.

Some important dates:

- African *Homo habilis* replaced by *Homo ergaster* 2-1.7 Mya
- **Out of Africa 1** : *H. ergaster* to Asia - 800 kya
- Appearance of *H. sapiens* in Africa 200 kya
- **Out of Africa 2** : *H. sapiens* to Eurasia, probably southern route – 130 - 100 kya

The recent origin of Homo sapiens and AMH (Anatomically Modern Humans)

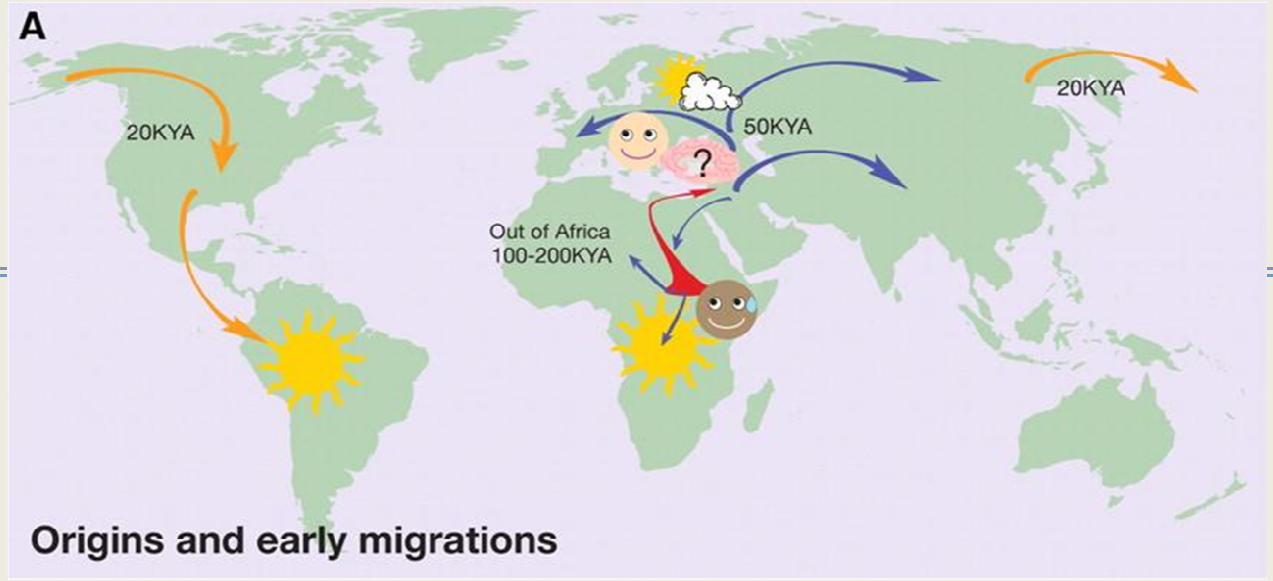


2. MIGRATIONS (GENE FLOW) OVERRODE ISOLATION (GENETIC DRIFT)

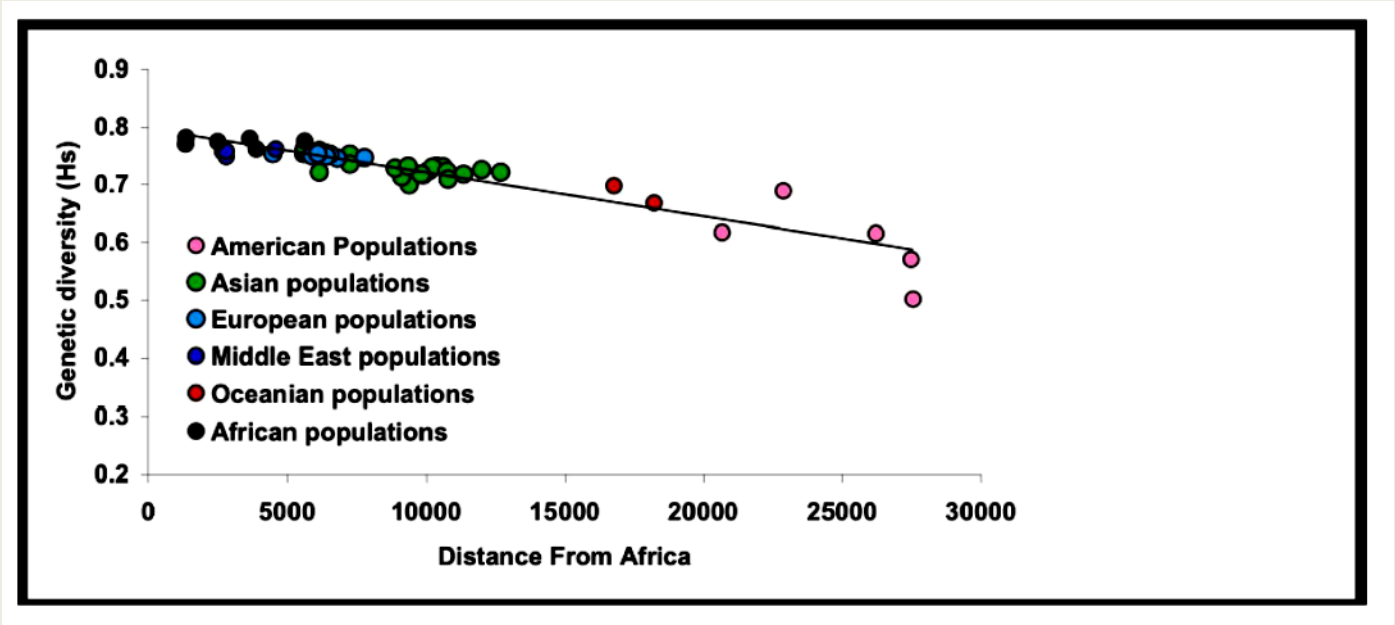
1. At the root of the Out of Africa 2 there is a strong demographic bottleneck

1. ALL HUMANS ARE DESCENDED FROM A SMALL AND HOMOGENEOUS FOUNDER GROUP

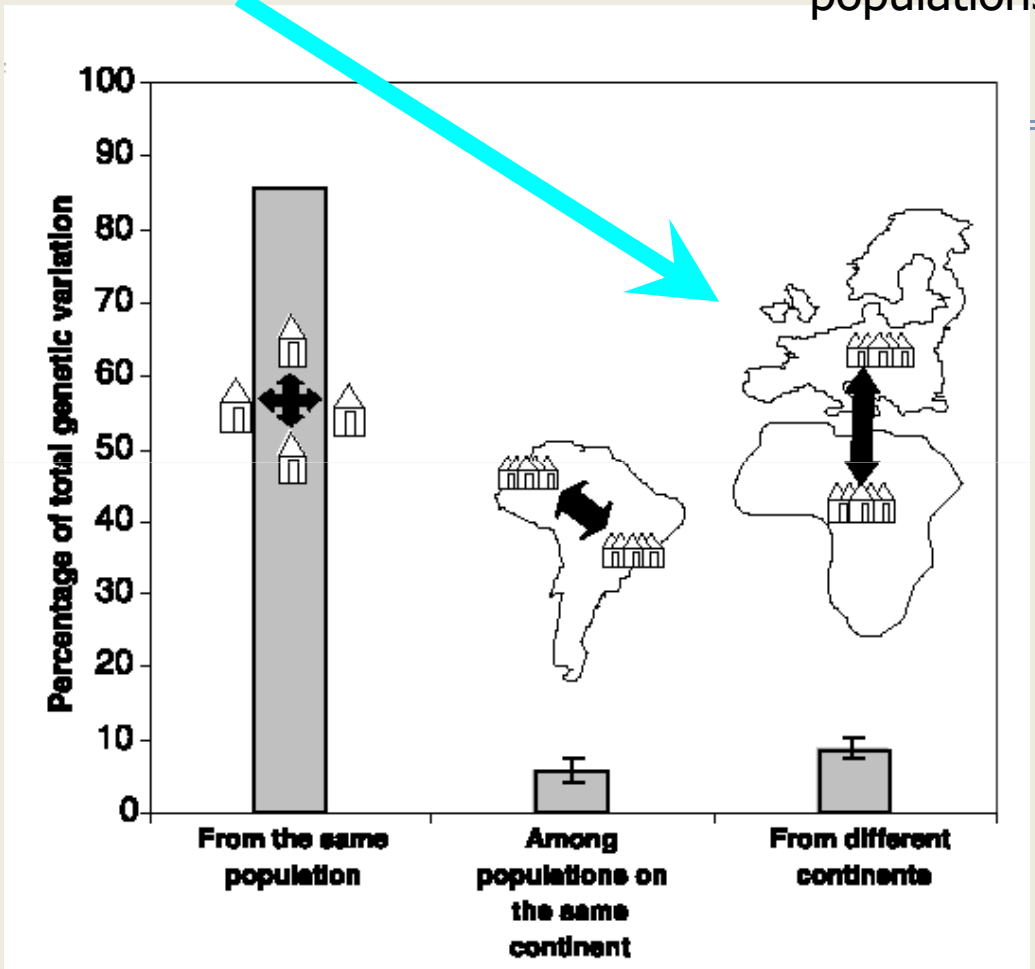
Origin and Spread of H. sapiens-The genetic perspective



A - *Modern human origins and early migrations*



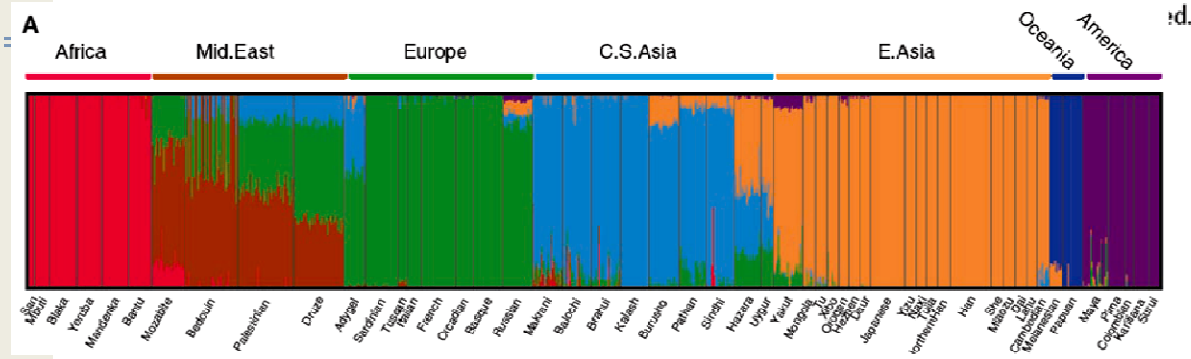
9-13 % of total allele frequency variance found between continental groups of populations

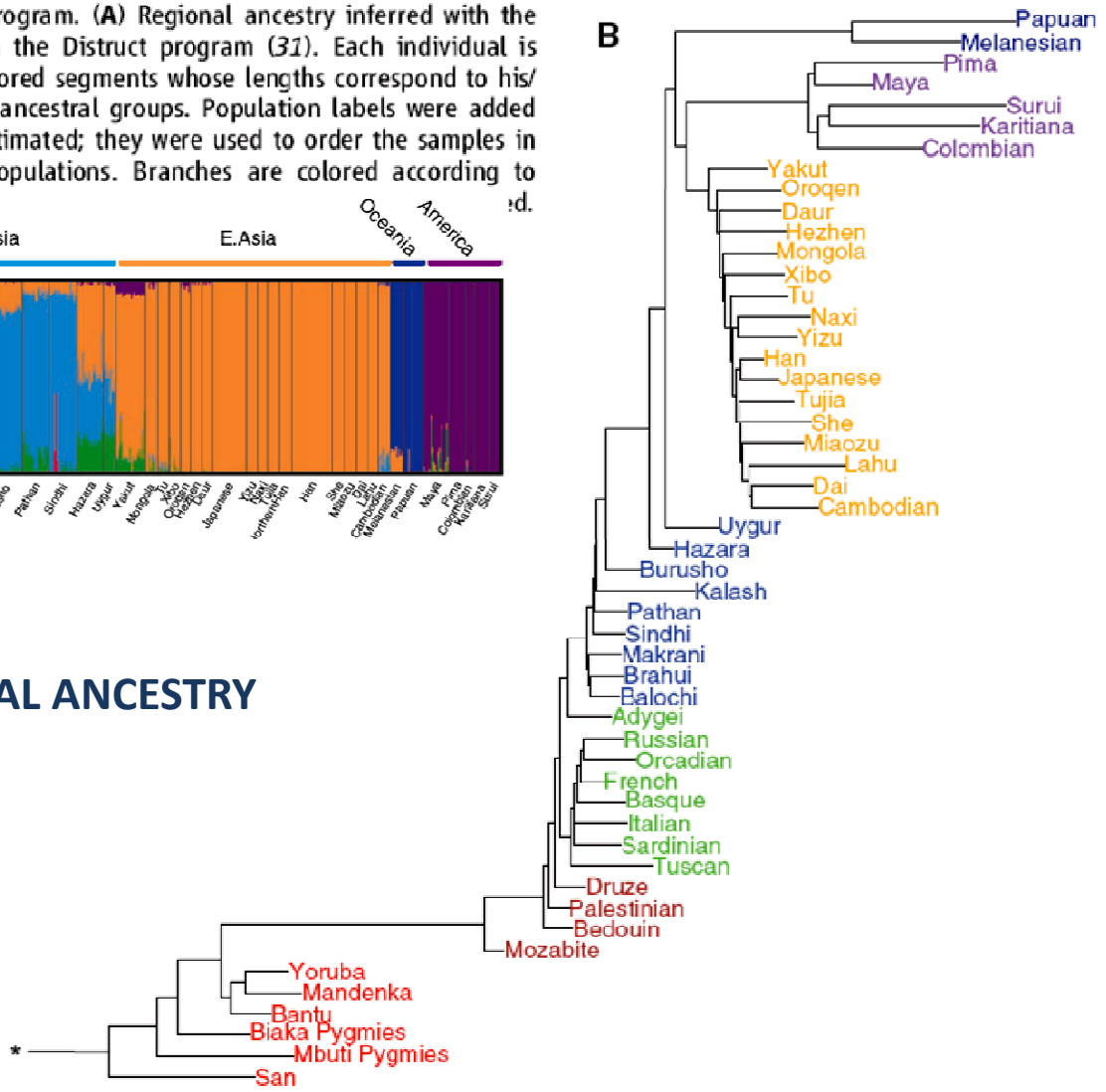


FROM "RACE"
TO

"BIOGEOGRAPHICAL ANCESTRY"

Fig. 1. Individual ancestry and population dendrogram. (**A**) Regional ancestry inferred with the *frappe* program at $K = 7$ (*13*) and plotted with the Distruct program (*31*). Each individual is represented by a vertical line partitioned into colored segments whose lengths correspond to his/her ancestry coefficients in up to seven inferred ancestral groups. Population labels were added only after each individual's ancestry had been estimated; they were used to order the samples in plotting. (**B**) Maximum likelihood tree of 51 populations. Branches are colored according to





INDIVIDUAL BIOGEOGRAPHICAL ANCESTRY

Current patterns of human genetic variation result not only from selective pressure, but also from population history and disentangling of these processes is challenging.

These patterns suggest that selection is often weak enough that neutral processes—especially population history, migration, and drift—exert powerful influences over the fate and geographic distribution of selected alleles.

INTERPRETING DEPARTURES FROM NEUTRALITY

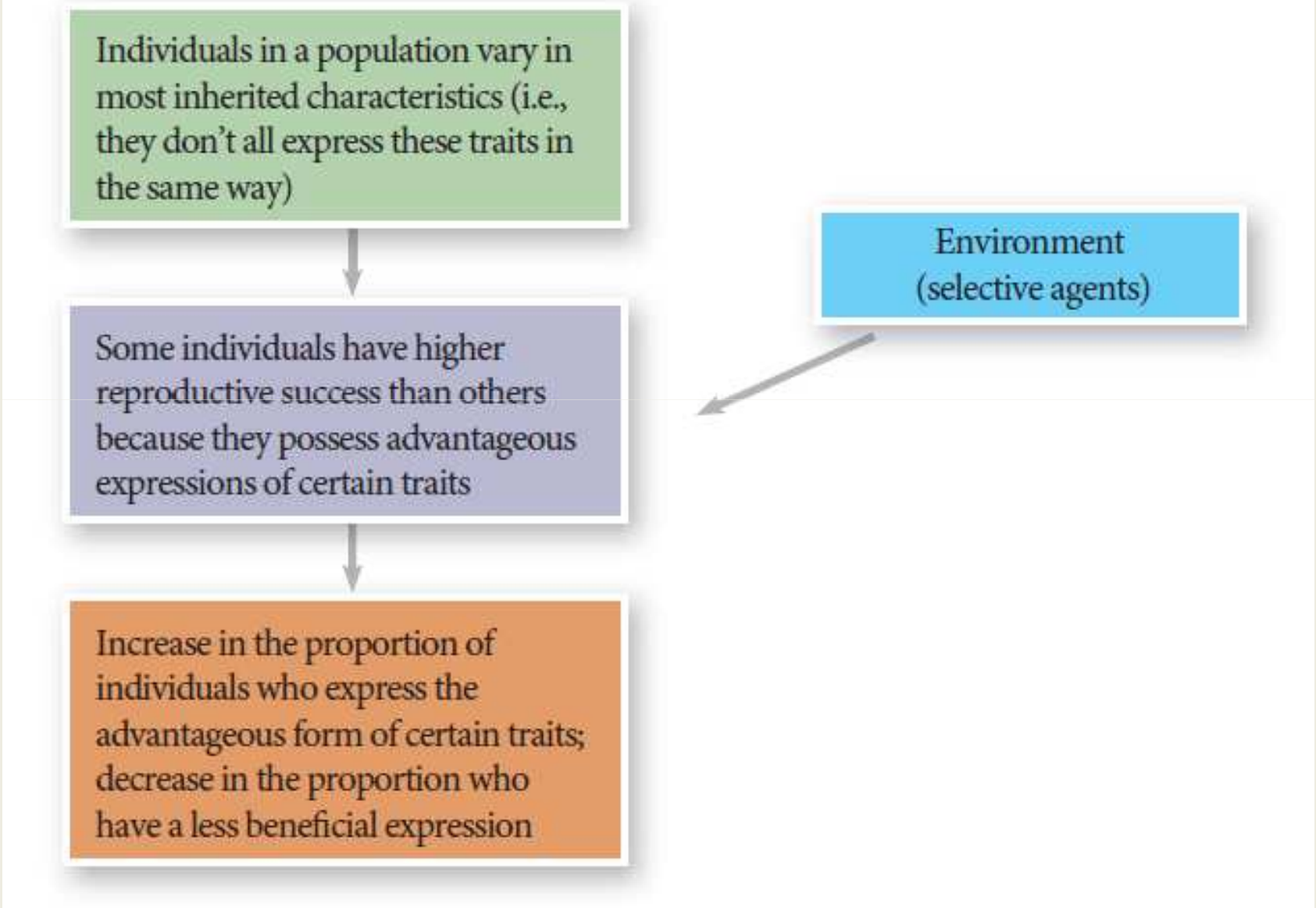
Demographic factors

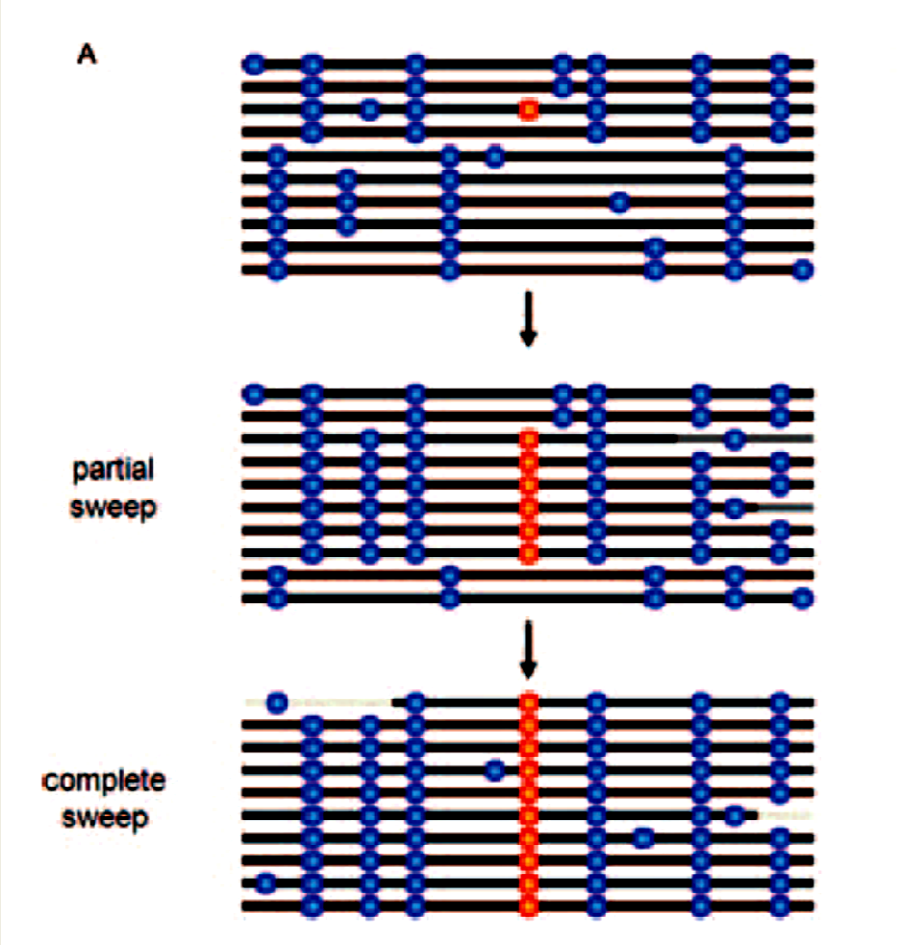
Affect in the same way all the genome

Selection

Affect in a different way different genes

The Mechanism of Natural Selection





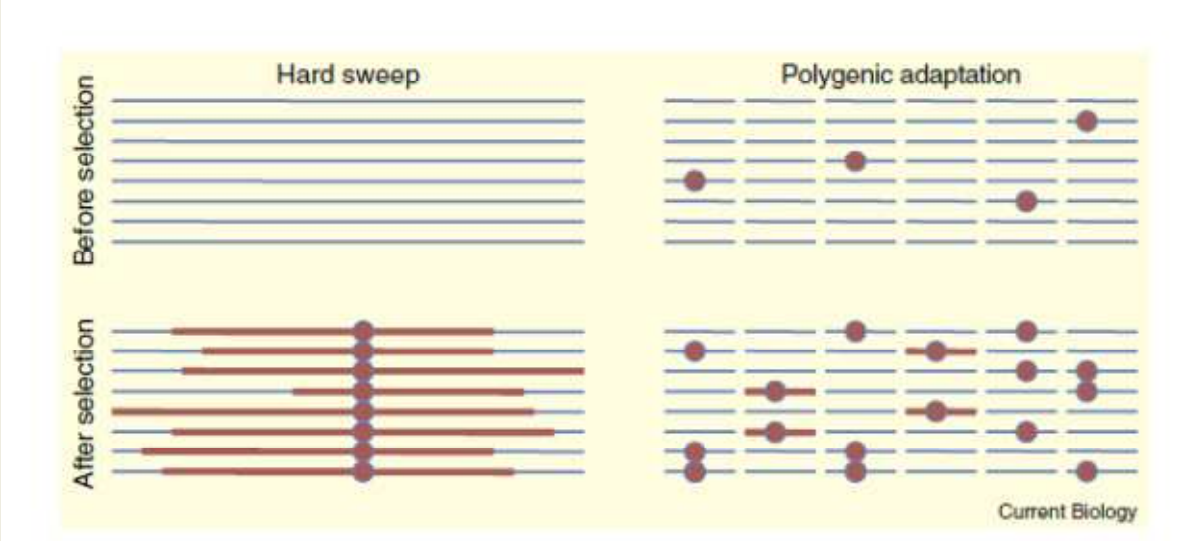
Intraspecific studies leaves a distinct mark on the pattern of genomic variation which due to **'selective sweep'**

When a mutation with a **beneficial fitness effect** arises in a population, natural selection will rapidly increase the frequency of the mutation to a high frequency (partial sweep) or to fixation (complete sweep), which **results in a reduction of diversity at and around the selected locus.**

Populations adapt to novel environments in two distinct ways:

- selection on pre-existing genetic variation (standing variation),
- selection on new mutations.

Selection on standing—rather than new—alleles, which afford a faster adaptive response to environmental change, may have played a prominent role in adaptation to new environments.

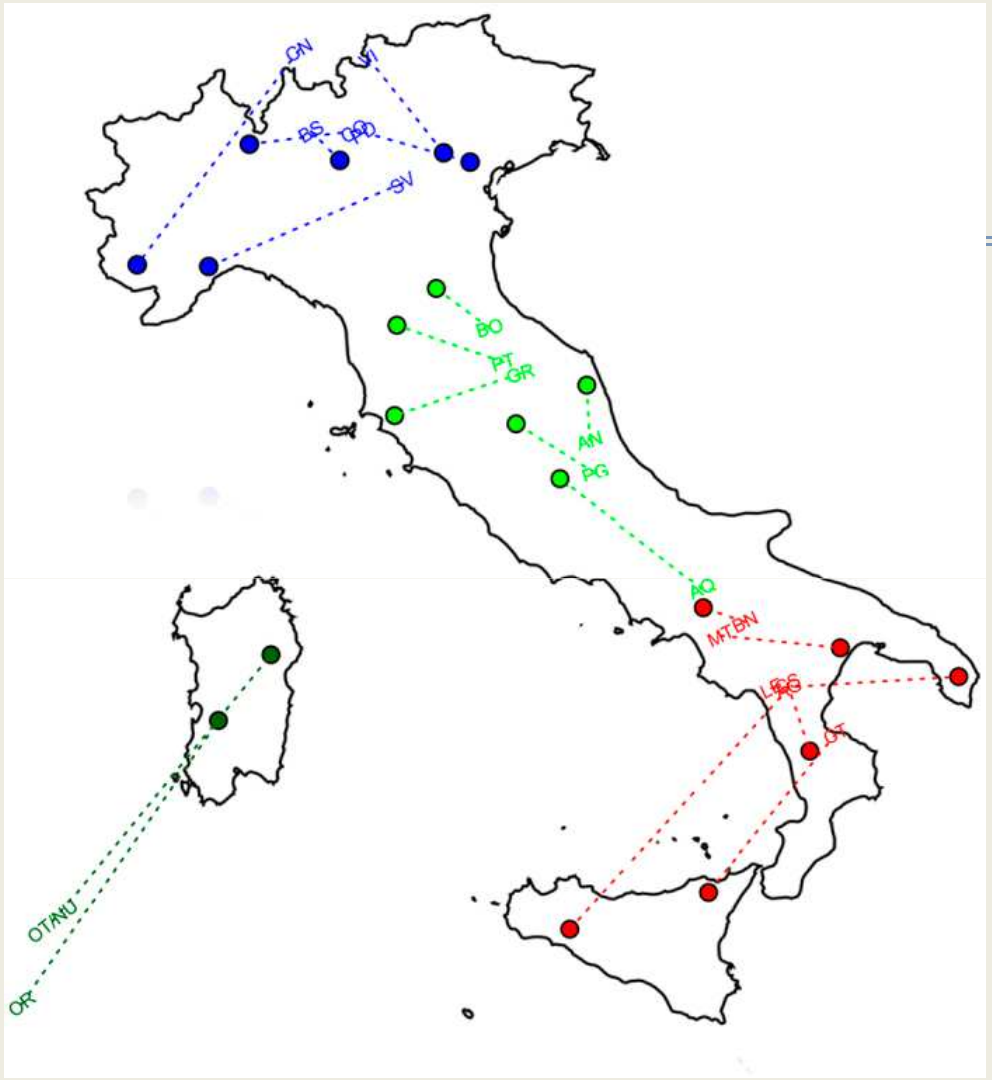


Selection acting on polygenic traits may lead to subtle shifts in allele frequency at many loci, with each allele making a small contribution to the phenotype. Detection of beneficial alleles that evolved under a polygenic selection model may be achieved by an approach that simultaneously consider the spacial distribution of the allele frequencies and the underlyining selective pressures.

The genetic variability of the Italian population (*Sazzini et al., 2016- SciRep*)

<u>The frequency of variants located in GENES involved in pathology varies across the Italian peninsula</u>

The role of 1) DEMOGRAPHY and of
2) LOCAL ADAPTATION



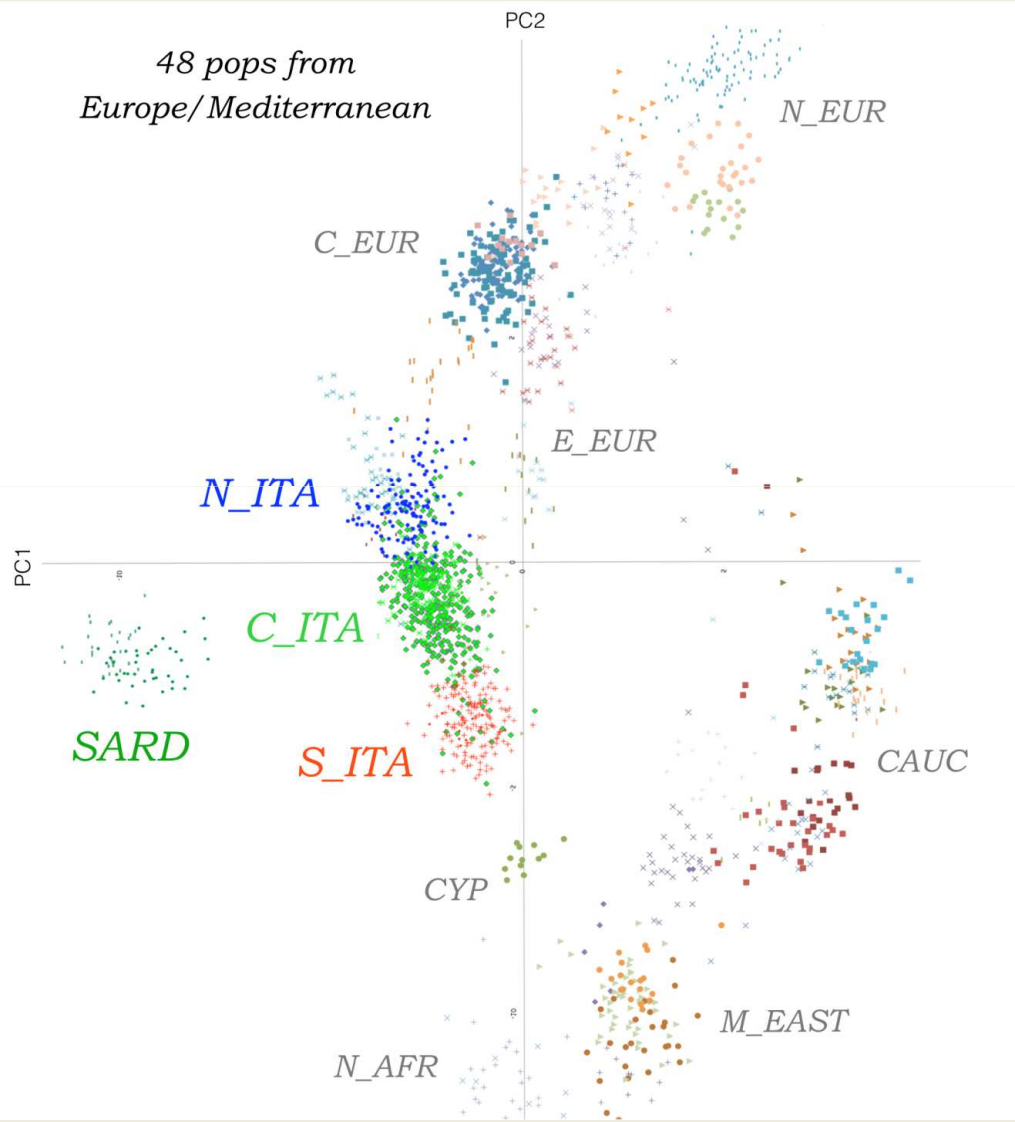
4 macro-areas with internal historical & cultural homogeneity

780 samples from 20 provinces (grandparents' criterion)

CoreExome chip Illumina

279,000 genome wide SNPs
245,000 exomic variants
19,000 disease associated variants

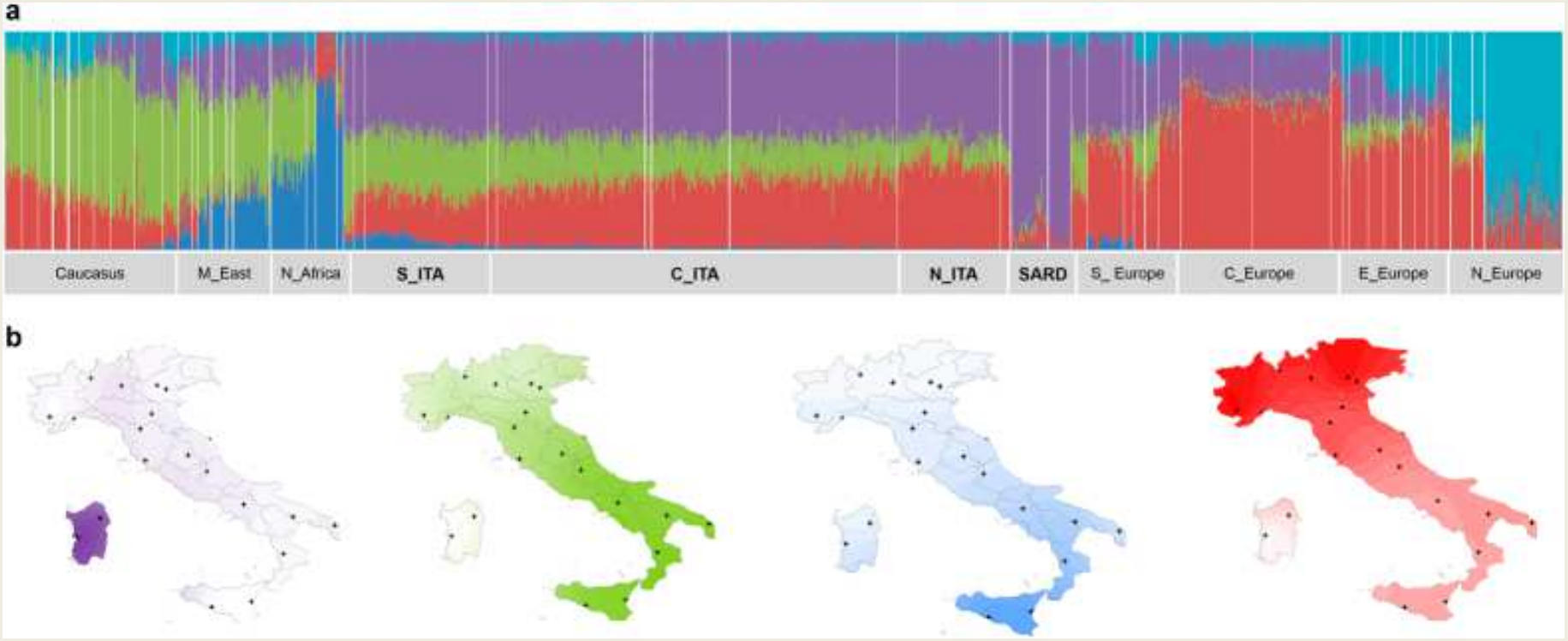
Inferring Admixture Events between Italian and European/Mediterranean populations



Principal component analysis

77,000 SNPs

ADMIXTURE analysis performed on the Italian population



The genetic background of the Italian population is the result of micro-evolutionary dynamics such as **admixture** and **migration** that occured at different time scales (**DEMOGRAPHY**)

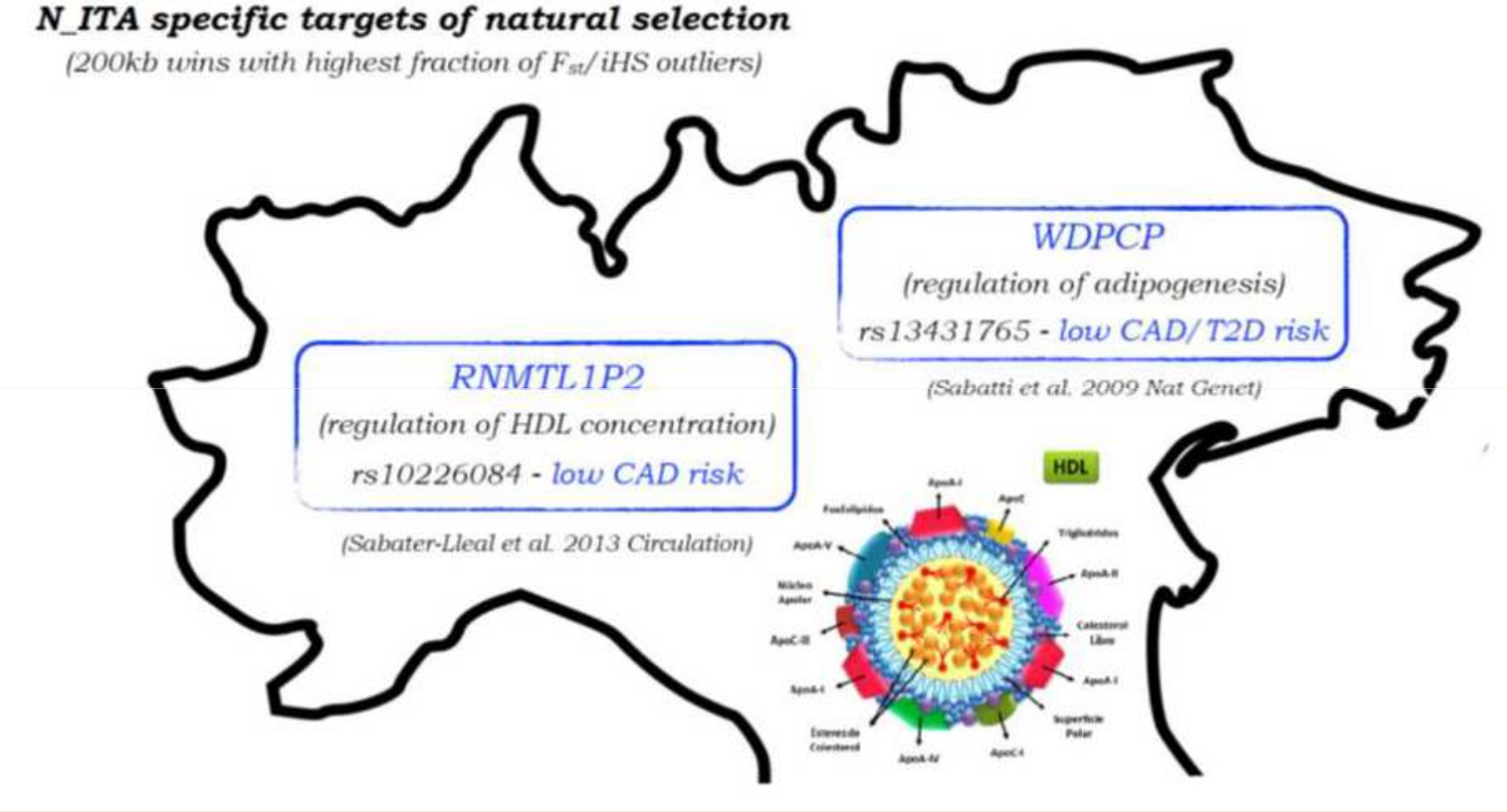
…not only **DEMOGRAPHY**

Single locus F_{st}

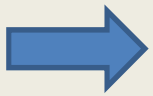
The most relevant findings emerged from **N_ITA and S_ITA** comparison, which showed significantly enriched Gene Ontology (GO) terms among the most differentiated genes being associated to processes of ***cell/neuron recognition and projection organization, as well as to cellular components devoted to signalling/trafficking (e.g. membrane rafts)***

→***TODAY*** ***this pathway play a role in the development of pathological conditions such as Alzheimer's, Parkinson's and cardiovascular diseases***

Signatures of Natural Selection on the Italian Genomes



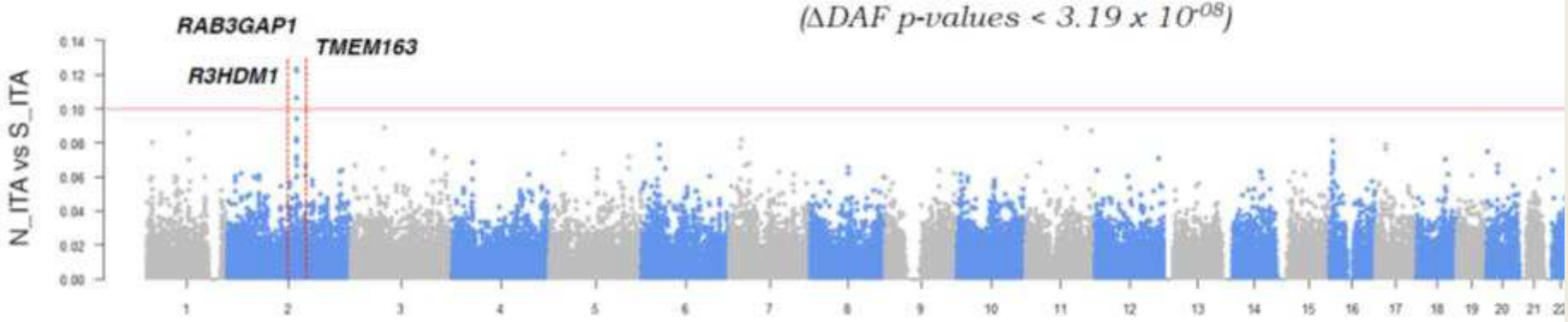
Climate and fat rich diets as selective pressures



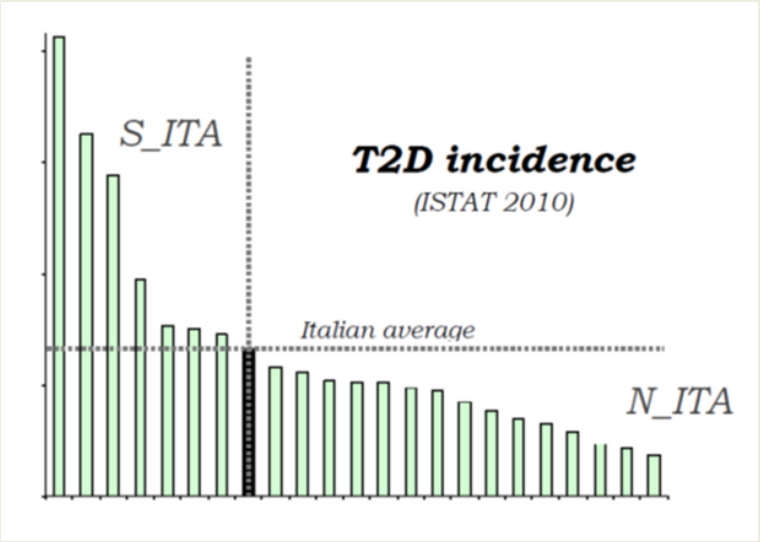
Modulation of lipid metabolism

Additional N_ITA specific targets of natural selection

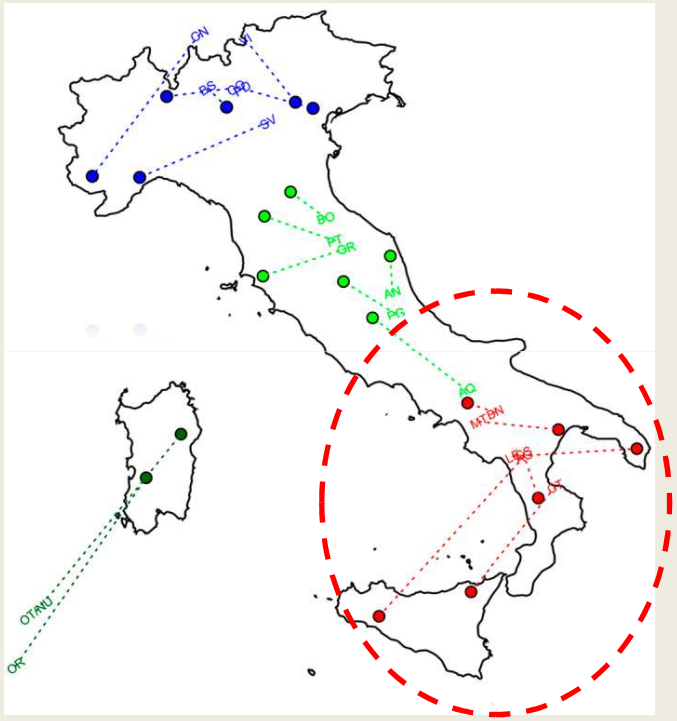
(ΔDAF p-values < 3.19 x 10^{-08})



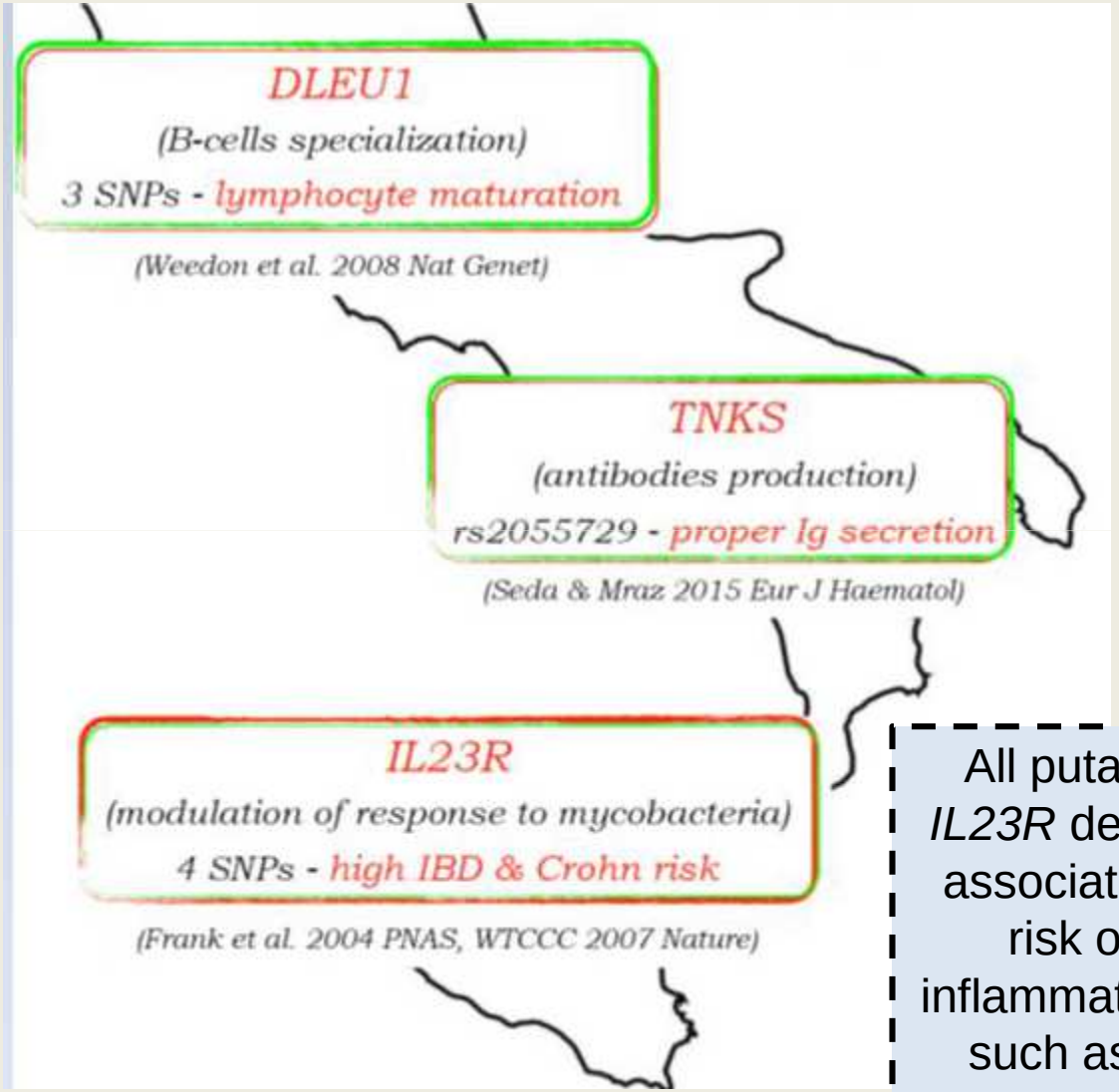
4 SNPs in low/moderate LD on 3 genes → *2 independent differentiation signals*



Signatures of Natural Selection on the Italian Genomes



The most relevant signatures of local selection in the South of Italy were observed in loci associated to **immune response** (***DLEU1*** lincRNA), reduced risk of myeloma and optimal antibodies production by B-lymphocytes (***TNKS*** enhancer) or able to modulate responses to mycobacterial infections **(*IL23R*)**

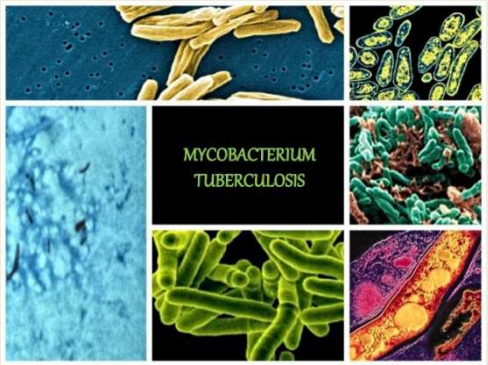


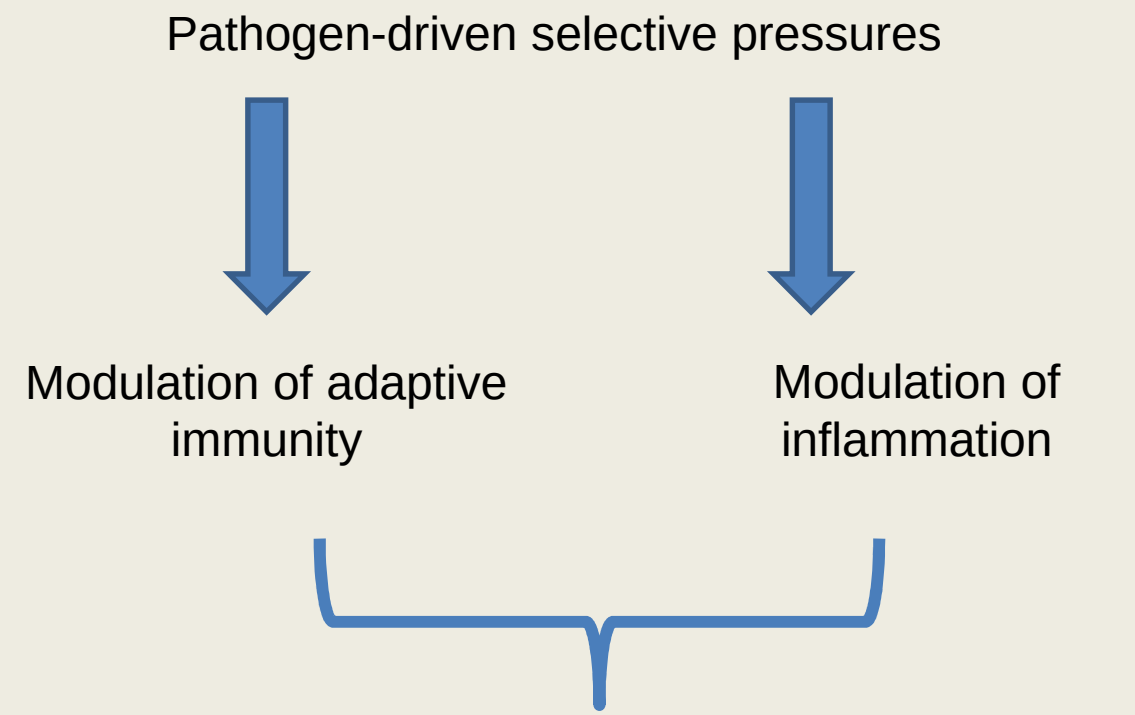
All putatively selected *IL23R* derived alleles are associated to increased risk of developing inflammatory phenotypes, such as inflammatory bowel and Crohn's diseases

PAST → part of such a genetic susceptibility might be related to alleles previously targeted by ***natural selection according to their capability to confer aggressive responses to pathogens***, but that became detrimental after the recent cultural shifts responsible for introduction of completely new immune-stimulatory epitopes in the diets of western societies.

specific infectious diseases, among which **tuberculosis** caused by *Mycobacterium tuberculosis* and **leprosy** caused by *Mycobacterium leprae*, could have represented selective pressures able to considerably shape Italian variation at this gene.

This hypothesis is compatible with the long coexistence between human populations settled along the Italian peninsula and such mycobacteria, as proved by the Italian paleoanthropological record that provided the earliest evidence of tuberculosis in the human species dated to around 5,800 years ago, as well as proofs of individuals affected by leprosy since approximately 2,400 years ago[24].





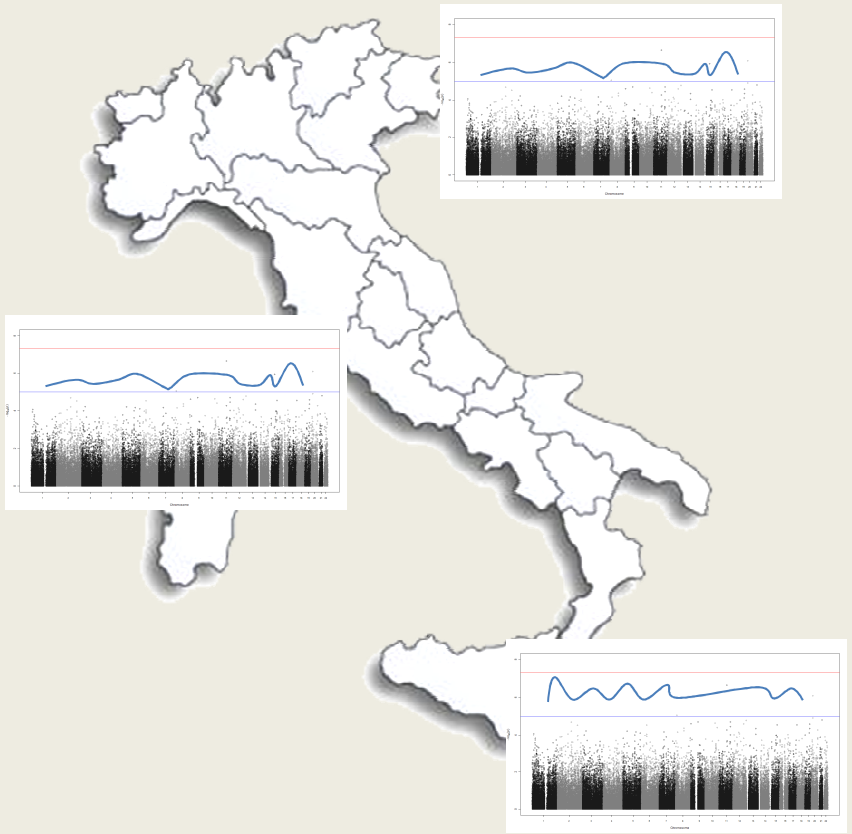
INCREASE RISK OF INFLAMMATORY DISEASE
IN **MODERN ENVIRONMENT**

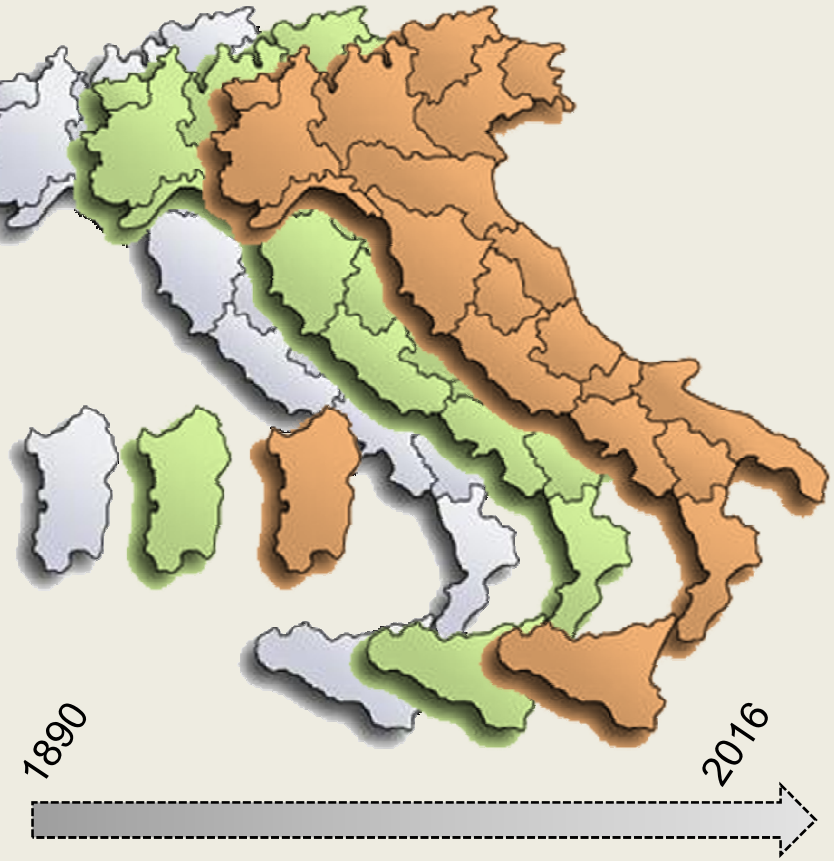
HEALTH STATUS or DISEASE

GENETICS BACKGROUND

+

CULTURE
(External environment)





Giuliani et al., 2017

Impact of demography and population dynamics on the genetic architecture of human longevity

The aim of this study is twofold:

(i) to test whether **past migrations, admixture and/or local adaptations** may have influenced the distribution of variants involved in human longevity in the Italian population;

(ii) to explore patterns of genomic variation in groups of individuals with different ages and, especially, in centenarians, to pinpoint possible **pleiotropic effects** and changing gene-environment interactions of longevity-related loci.

Aging (Albany NY). 2018 Aug 8;10(8):1947-1963. doi: 10.18632/aging.101515.

Impact of demography and population dynamics on the genetic architecture of human longevity.

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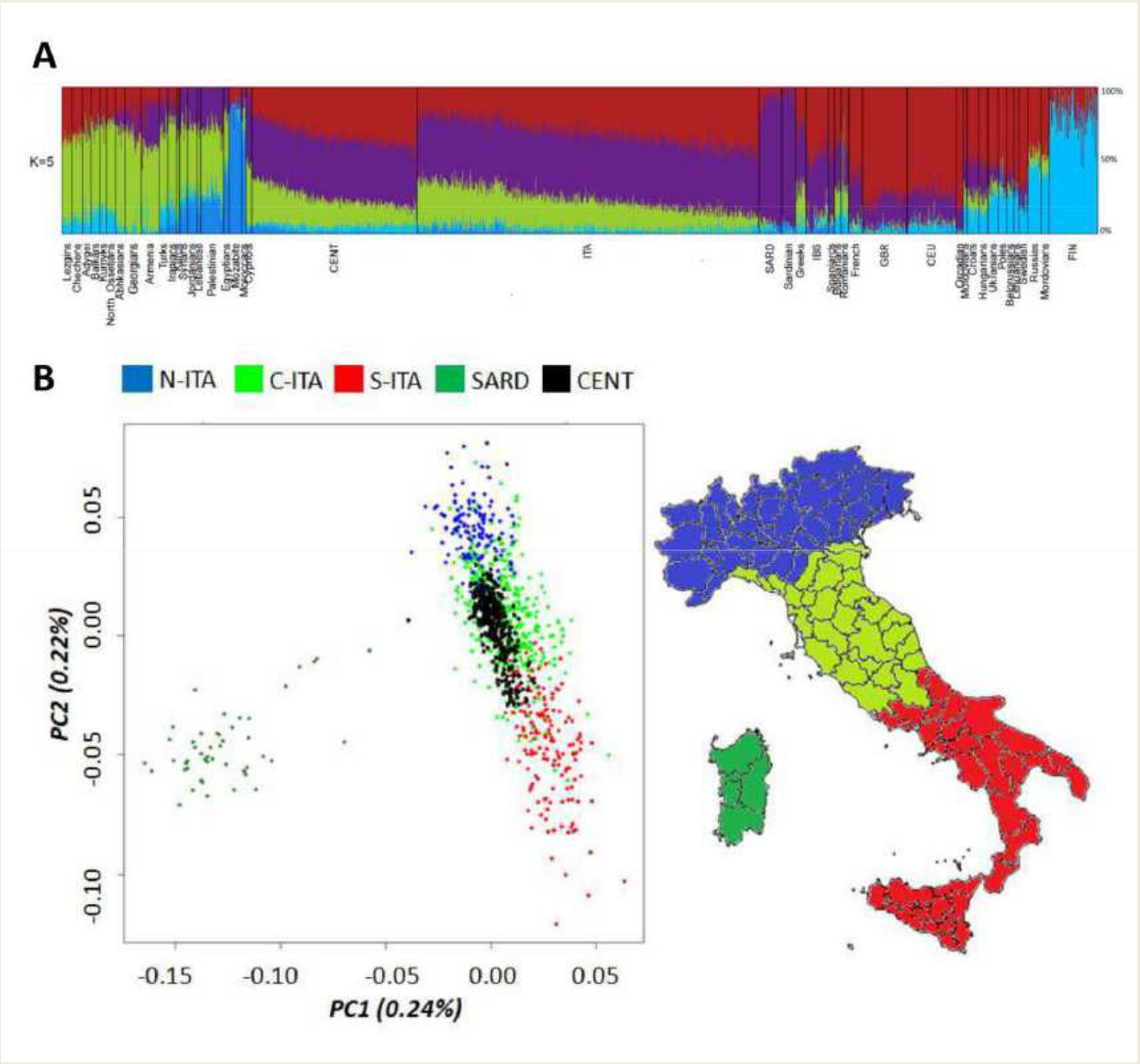


(A) Ancestry proportions at K = 5 estimated by ADMIXTURE analysis performed on Italian centenarians and controls, as well as on 50 Mediterranean and European populations. (B) First and second PCs calculated on the Italian general population (controls). Centenarians were projected as a supplementary group. Individuals from Northern Italy are indicated in blue, from Central Italy in green and from Southern Italy in red. Individuals from Sardinia are displayed in dark green.

i) A possible explanation for such a peculiar pattern is that recent ancestors of most centenarians born in Northern Italy have previously migrated from central/southern regions.

ii) A second explanation is instead that a set of genetic variants sufficiently ancient to be distributed across the entire Italian population, but present at higher frequency in central/southern groups with respect to northern ones, could contribute to increase probability to develop the longevity phenotype and is thus enriched in centenarians irrespectively of their recent micro-geographical origin.

a) Centenarian genomes are enriched for an ancestral component likely shaped by pre-Neolithic migrations

b) Centenarians born in Northern Italy unexpectedly clustered with controls from Central and Southern Italy suggesting that → Neolithic gene flow did not favour longevity in this population;

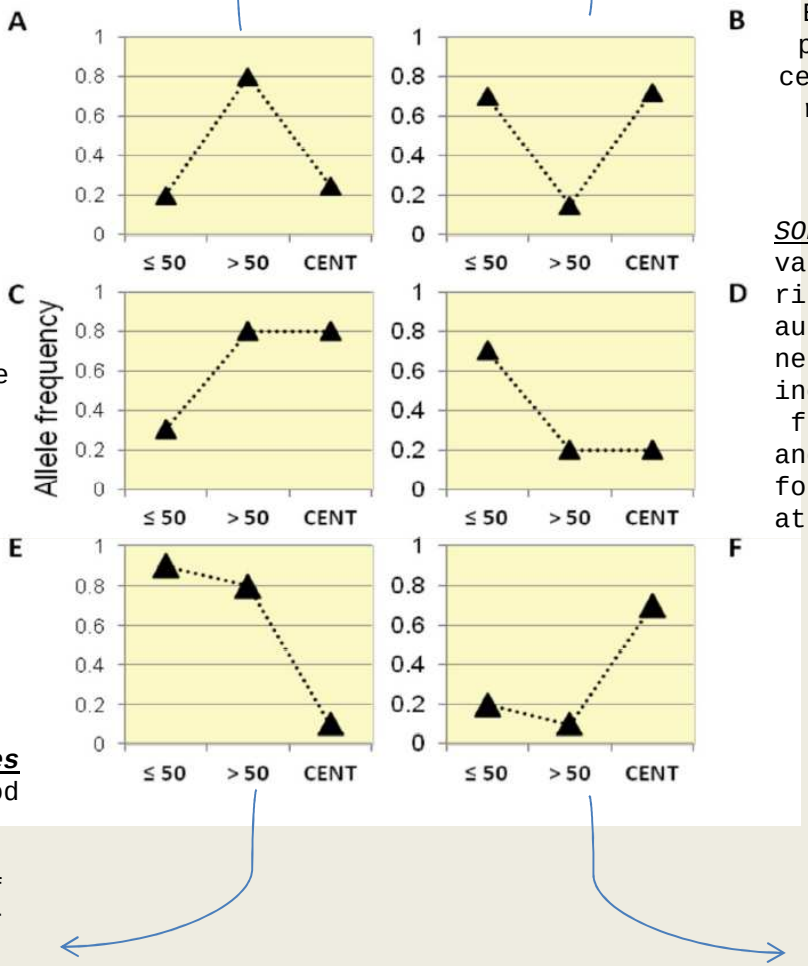
Pathway analyses by means of i-GSEA4GWAS.
Four KEGG pathways were thus ranked as significantly enriched (FDR ≤ 0.05):

1) inositol phosphate metabolism,
2) homologous recombination,
3) **linoleic acid metabolism**,
4) drug metabolism cytochrome P450

ESRRG (estrogen related receptor gamma) → presence of a trade-off between **tumor suppression and brain regeneration** influenced by *ESRRG*. → it may differentially influence survival at the different age intervals.

ATP8 gene (phospholipid transport in the cell membrane) : This represents an example of pleiotropy → in the last decades of life individuals with variants associated to low ATP8B4 expression reduced the probability of Alzheimer disease onset.

CLSTN2, ANO3 and TOMM40 genes associated to diastolic blood pressure, high density lipoprotein cholesterol measurement, high levels of triglycerides and Alzheimer diseases

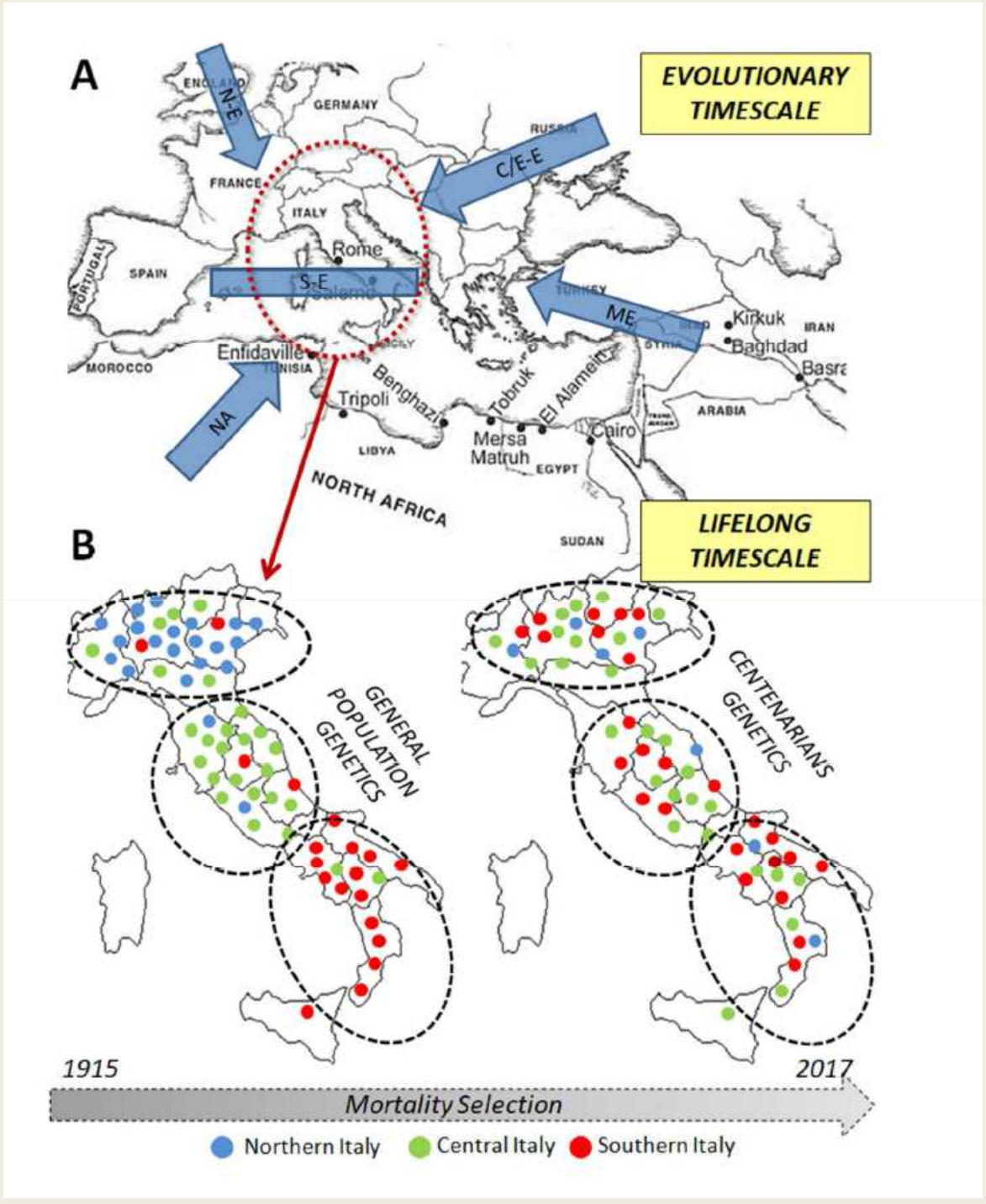


EPCAM gene- These SNPs show a differential impact on the expression of two genes, MSH (recognizes errors in the genome sequence during replication) and EPCAM (regulation of apoptotic processes) → trade-off between cell proliferation, apoptosis and repair mechanisms in different tissues.

SORCS2 and *SORCS3* genes, its variants are considered as genetic risk factors for sporadic and autosomal dominant forms of neurodegenerative diseases, including Alzheimer's disease, frontotemporal lobar degeneration, and Parkinson's disease, as well as for type 2 diabetes mellitus and atherosclerosis

ASIC2 locus. This gene seems to play a role in neurotransmission and it has been described as a plausible candidate locus in a meta-analysis of four GWASs of survival to age 90 years or older and in a recent paper focused on Chinese centenarians

d) lifelong non-monotonic changes in the frequency of several alleles revealed different pleiotropy and trade-off mechanisms crucial for longevity



Overview of the diachronic approach used to combine information about processes occurred at different timescales (i.e. evolutionary and lifespan ones) in the study of the genetics of human longevity.
(A) Northern European, N-E; Central/Eastern European, CE-E; Southern European, S-E; Middle Eastern, ME; Northern African, NA.
(B) Each dot represents an individual in the general population - left - and in centenarians - right. The colour indicates the recruitment center and the position in the map indicates the genetic similarity)

The complexity of APOE

Table 2. The Complexity of *APOE* Gene Variants

Macro and microevolutionary background
APOE-e4 is the ancestral allele typical of modern humans;
APOE-e2 and APOE-e3 evolved ≈200 000–300 000 y ago;
APOE-e4 is associated with improved cognitive function in Amazonian forager-horticulturalists with a high parasite burden;
High frequency of *APOE*-e4 was maintained in the population because it confers a beneficial effect during infections and in the environment where pathogens were more prevalent and the first cause of mortality (data on a rural Ghanaian population);
Today geographic distribution
APOE-4 showed a cline in Europe (from 20% in North Europe to 6/7% in Southern Europe)
e4 allele in human populations follows a sort of U-shaped latitudinal trajectory, high frequencies (up to ≈40%–50% of the population) in equatorial and high latitudes and low frequencies in middle latitudes
Involvement in physiological traits
Lipid metabolism, regulating production, conversion
APOE-e4 is associated with high cholesterol
Clearance of lipoproteins
It is expressed in different tissues, macrophage, adipose tissue, nervous system, and liver
APOE-e4 allele had significantly higher levels of mean luteal progesterone than women with genotypes without ApoE4, which indicates higher potential fertility
In mice, APOE-4 carriers are more vulnerable to a dietary deficiency in omega-3 fatty acids and cognitive decline
High levels of physical activity reduce disease risks in ε4 carriers
Spatial memory of transgenic mice carrying human forms of these proteins and find that it is impaired in mice with apoE4 but not those with apoE3
Involvement in pathological traits
APOE-e4 is associated with Alzheimer disease (AD) and cardiovascular diseases (APOE-e4)
People with APOE-e3 o APOE-e2 have later AD onset than APOE-e4
Longevity
APOE-e4 is negatively associated with longevity in many studies and meta-analysis on human longevity
The gene variants identified in these regions are located also in TOMM40 and APOC1

APOE indicates apolipoprotein E.

Circulation Research

September 14, 2018
Vol 123, Issue 7

Cardiovascular Aging Compendium

Genetics of Human Longevity Within an Eco-Evolutionary Nature-Nurture Framework

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