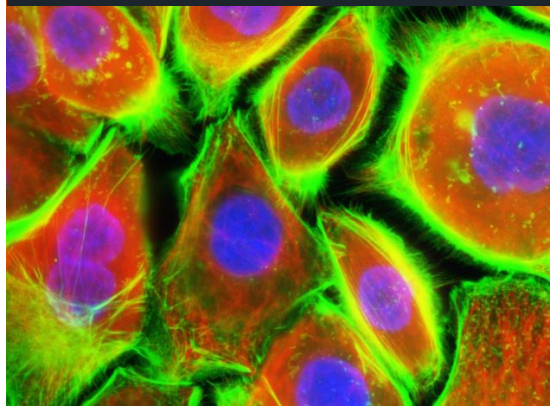
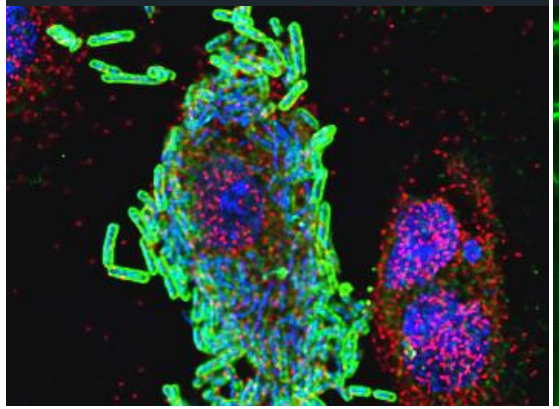
Human evolution and susceptibility to complex diseases: a genomic tale

Luísa Pereira
Genetic Diversity Group

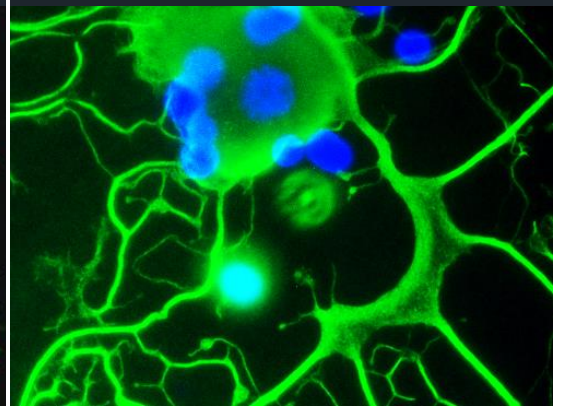
Cancer
23 research groups



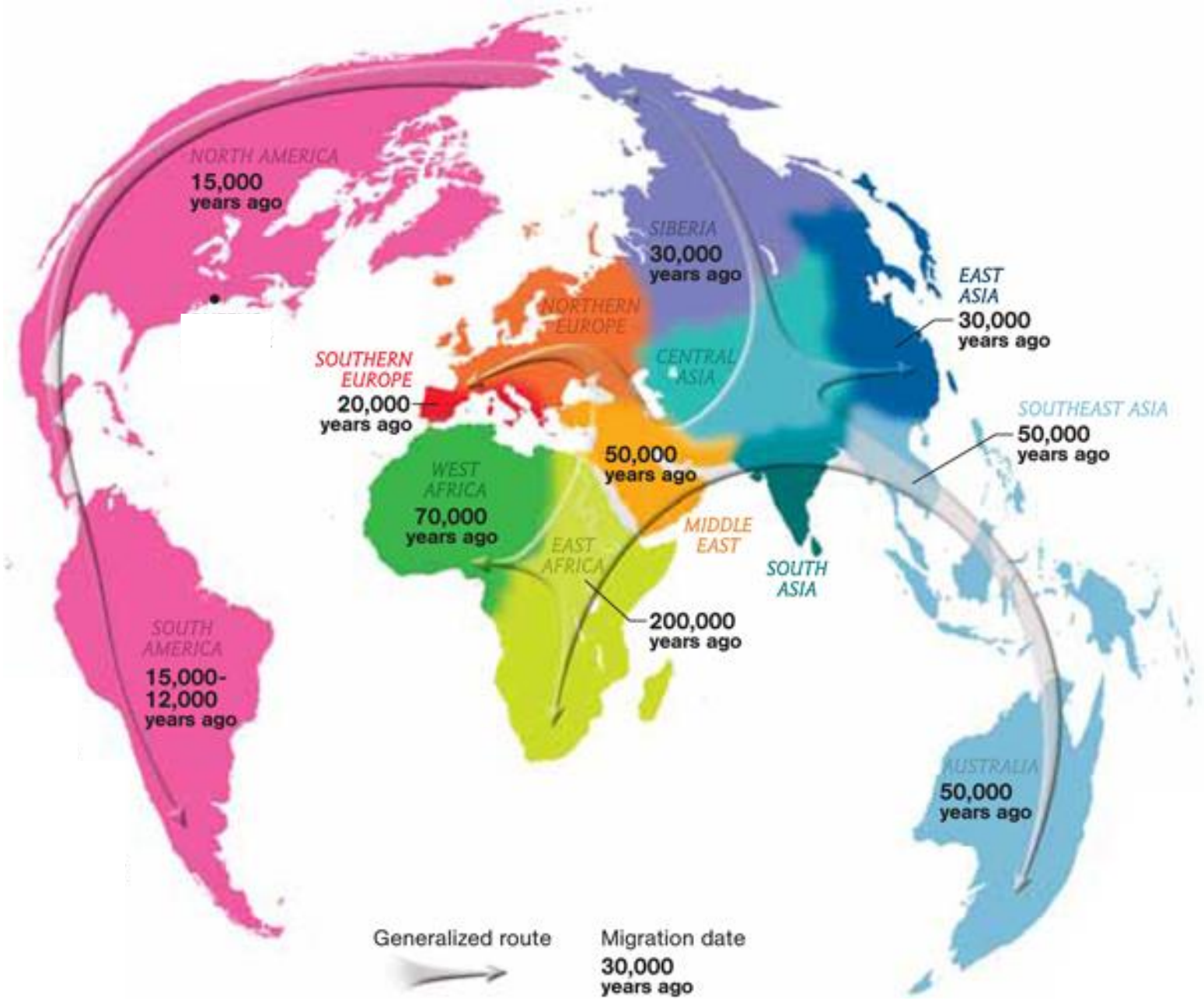
Infection, Immunity and Regeneration
25 research groups

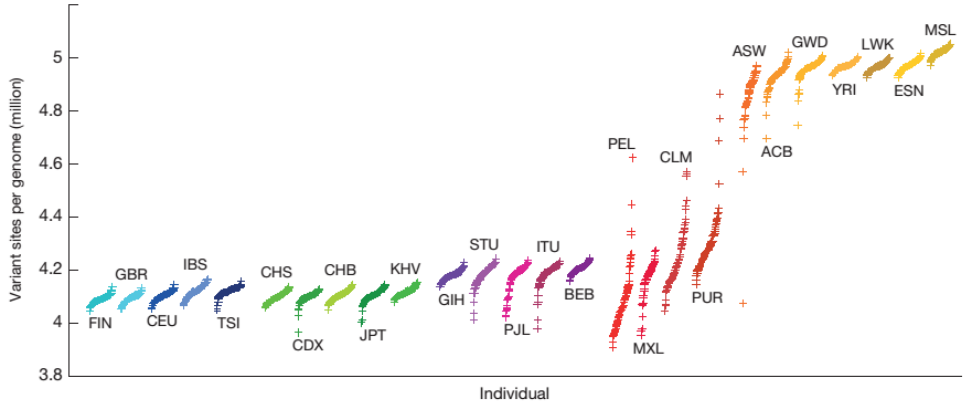


Neurobiology and Neurologic Disorders
18 research groups

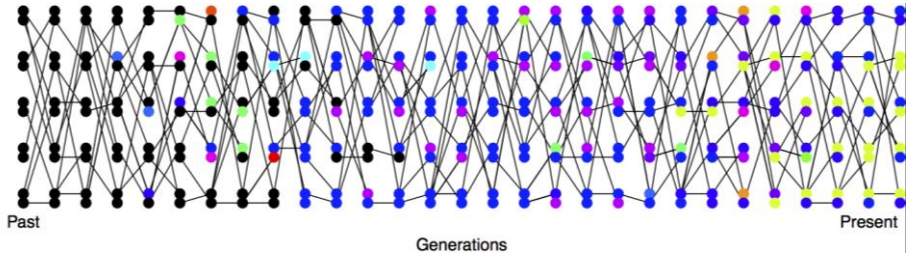


Worldwide genetic diversity – human migrations

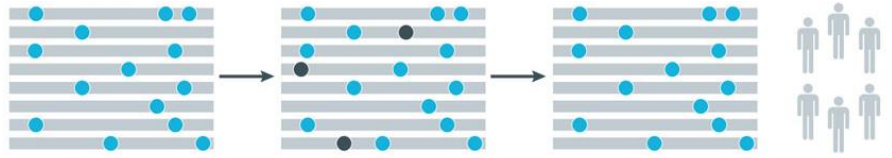




Drift



Negative selection

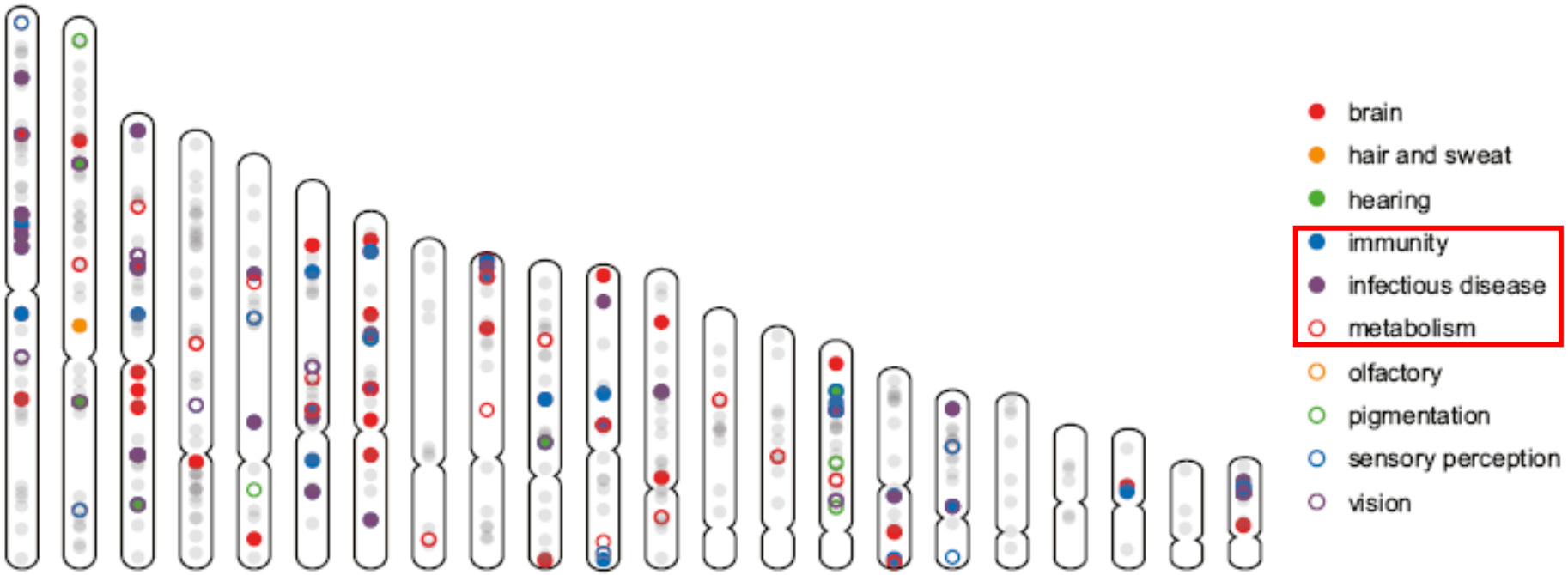


Positive selection or adaptation

Positive selection – immune and food-related

Grossman et al. (2013) Cell 152:703-713

1000 Genomes
CEU, YRI and CHB+JPT



INSTITUTO
DE INVESTIGAÇÃO
E INOVAÇÃO
EM SAÚDE
UNIVERSIDADE
DO PORTO

Rationale of an evolutionary approach in evaluating susceptibility to complex diseases

- Thousands of years of evolution selected the best fit biological responses

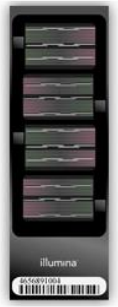
- If we understand the biological mechanisms, we can mimick them for therapeutical approaches

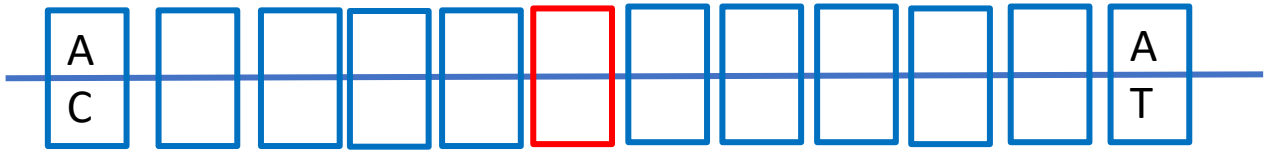
- Even if the selection event took place in one population group, it can be extrapolated to all humans

INSTITUTO
DE INVESTIGAÇÃO
E INOVAÇÃO
EM SAÚDE
UNIVERSIDADE
DO PORTO

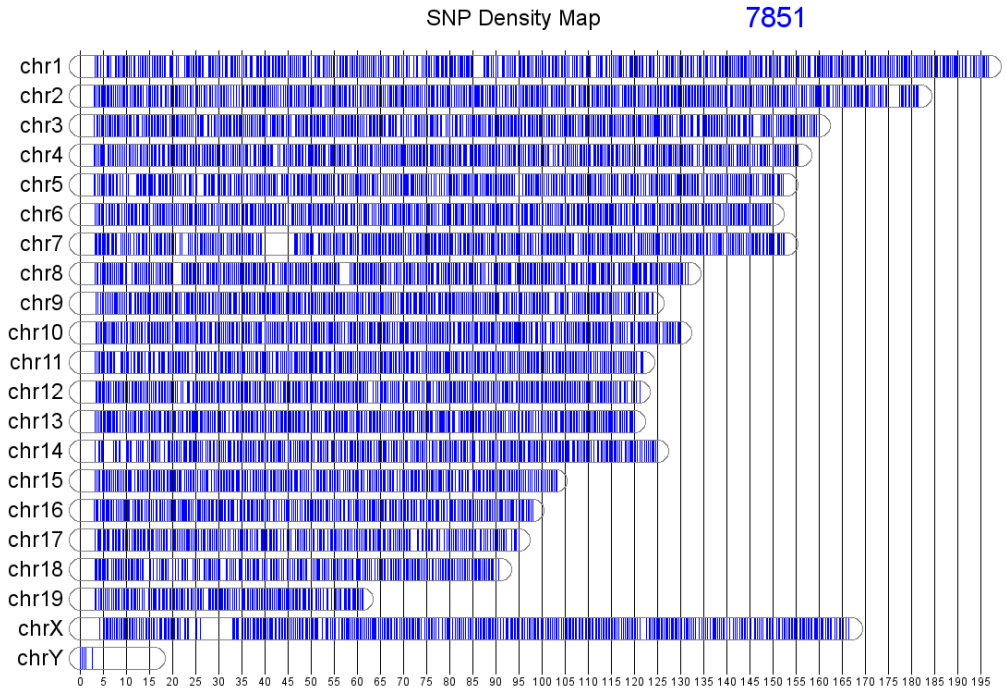
Dengue fever – Admixture mapping

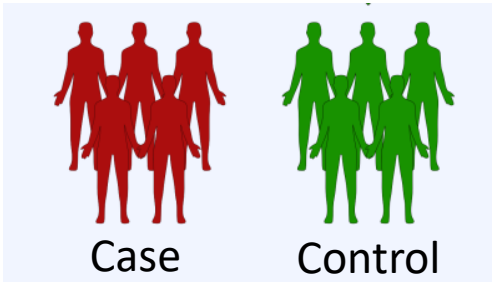
Array technology

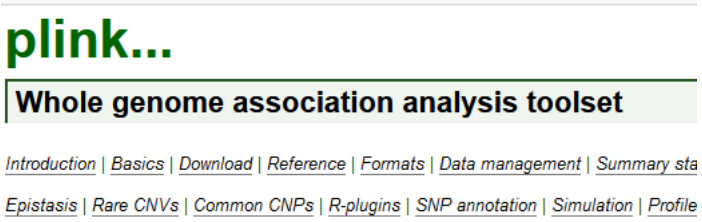




Linkage disequilibrium
Tag markers – Causative marker



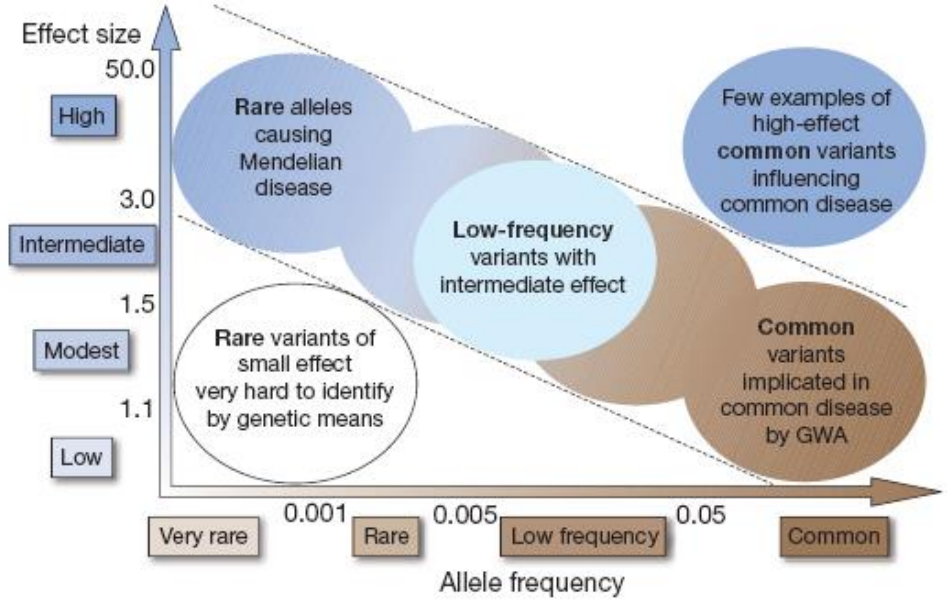




Genome Wide Association Study (GWAS)

INSTITUTO
DE INVESTIGAÇÃO
E INOVAÇÃO
EM SAÚDE
UNIVERSIDADE
DO PORTO

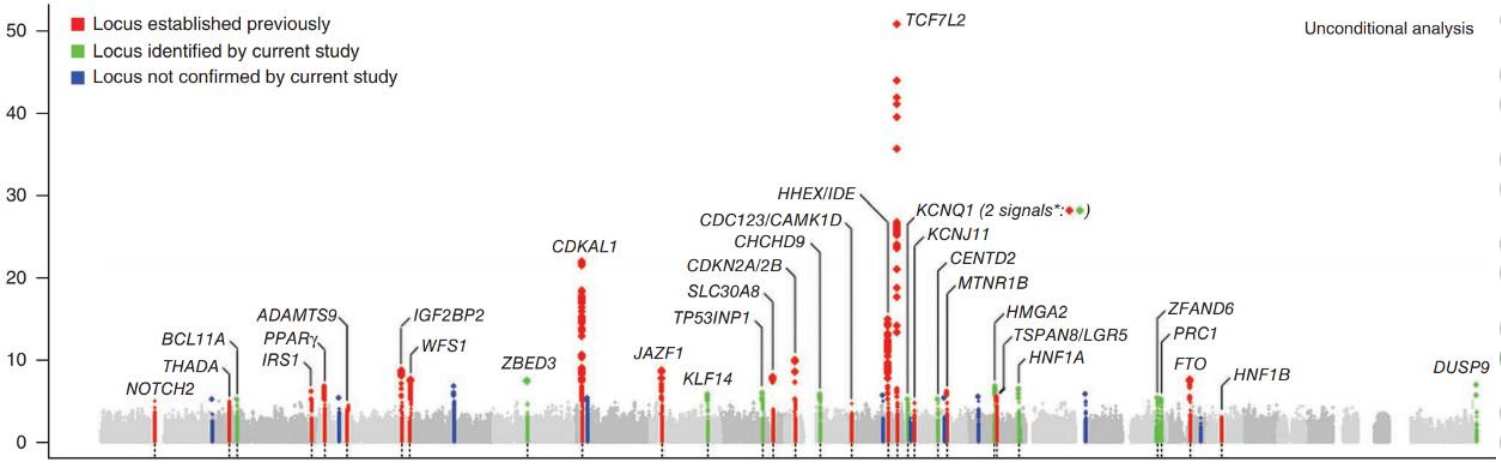
Statistical burden in complex diseases evaluation



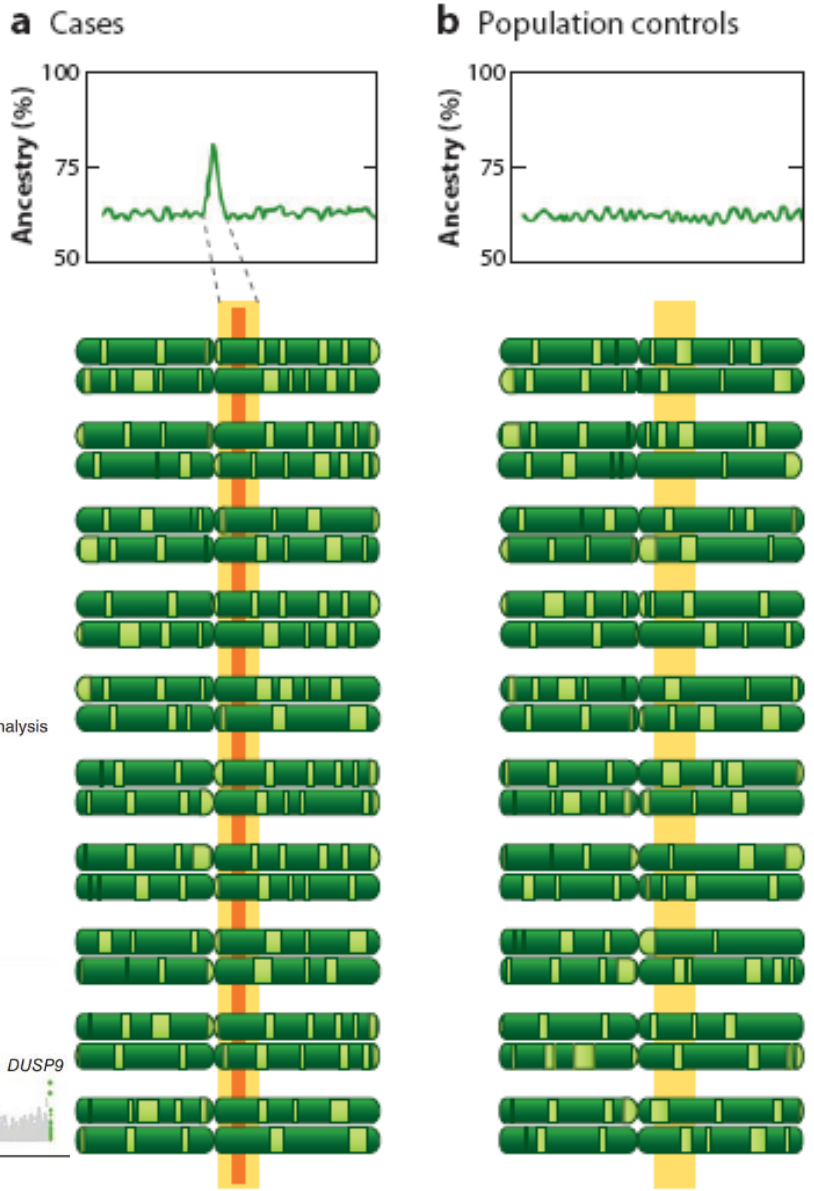
Traditional GWAS

Statistical burden: 0.05/600,000 = 8.33×10^{-8}

Thousands of individuals must be studied



Admixture mapping

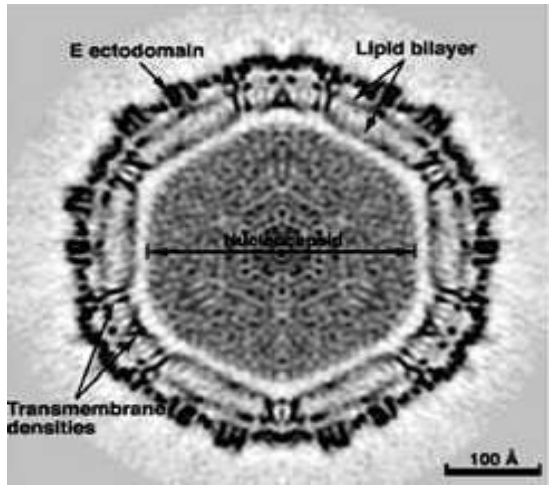


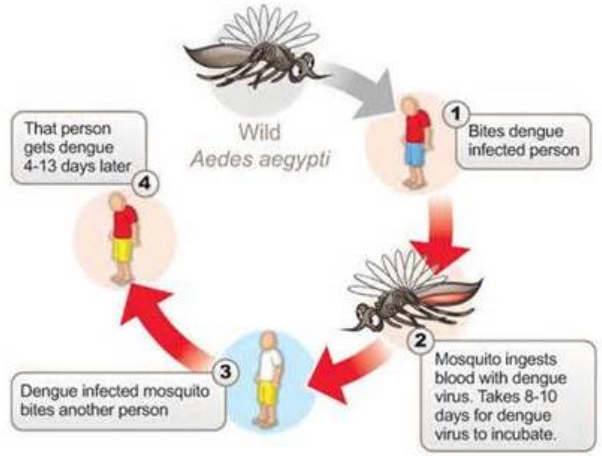
Statistical burden: 0.05/180 = 2.7×10^{-4}

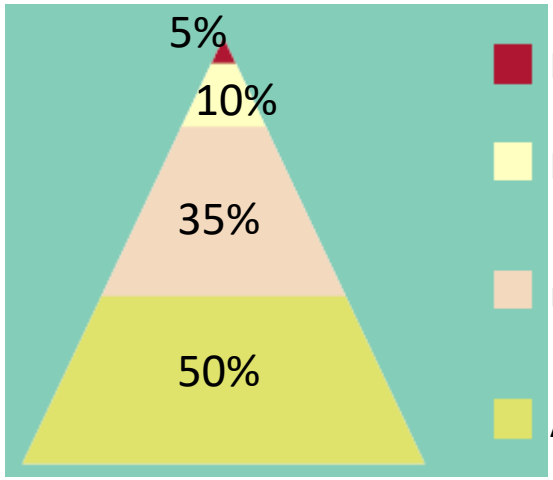
Sample size decreases to hundreds

More interesting in terms of population genetics

Flavivirus - 4 serotypes



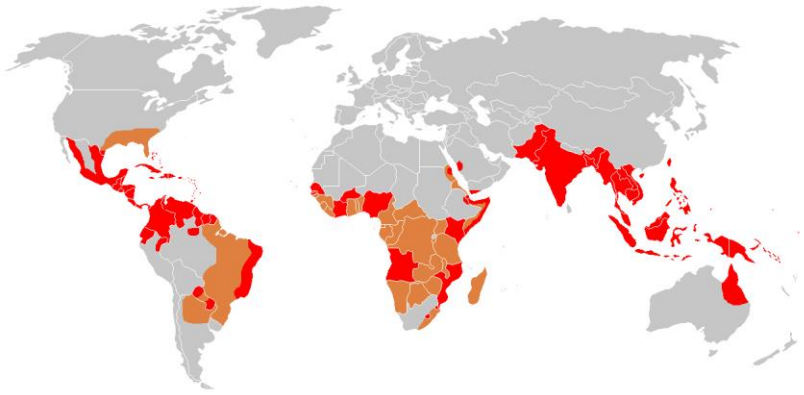




PLOS PATHOGENS

100 million cases per year – high health burden

Epidemiologic evidence in Cuba: dark-skinned people presented less severe form and died less of dengue disease than light-skinned people



. red - epidemic dengue and presence of *Aedes aegypti*
. brown - only *Ae. aegypti*

2.5 million SNP Illumina array

RESEARCH ARTICLE

OSBPL10, *RXRA* and lipid metabolism confer African-ancestry protection against dengue haemorrhagic fever in admixed Cubans

Beatriz Sierra[1☯]*, Petr Triska[2,3,4☯], Pedro Soares[3], Gissel Garcia[1], Ana B. Perez[1], Eglys Aguirre[1], Marisa Oliveira[2,3,4,5,6], Bruno Cavadas[2,3], Béatrice Regnault[5], Mayling Alvarez[1], Didye Ruiz[1], David C. Samuels[7], Anavaj Sakuntabhai[6], Luisa Pereira[2,3,8]*, Maria G. Guzman[1]

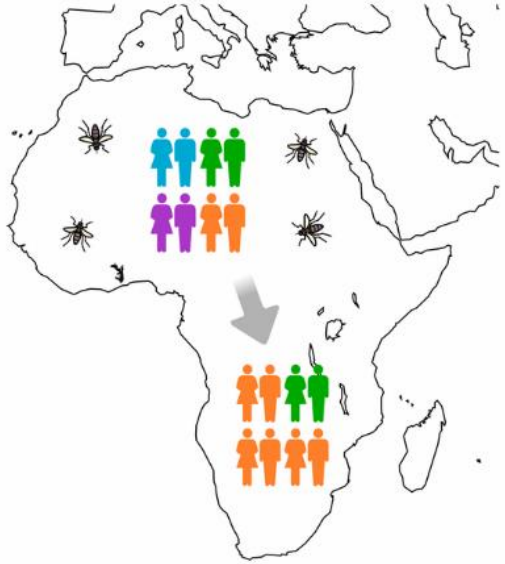
Table 1. Odds ratios of the African ancestry influence in DHF phenotype when compared to asymptomatic subjects, in Cuba in general, only Havana city and in Colombia.

	Odds ratio		
	1% African ancestry	50% African ancestry	100% African ancestry
Cuba	0.979	0.396	0.151
Havana	0.920	0.045	0.012
Colombia*	0.962	0.204	0.042

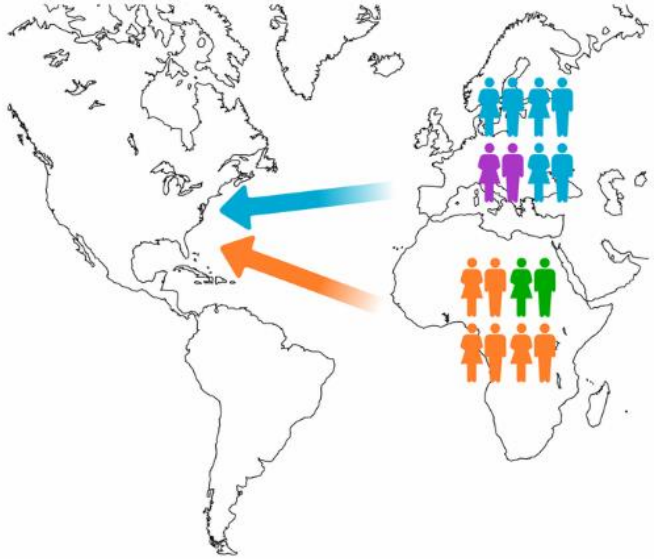
* From [11].

Admixed populations acquired selected variants that emmerged by adaptation in other geographical regions – ADAPTIVE ADMIXTURE

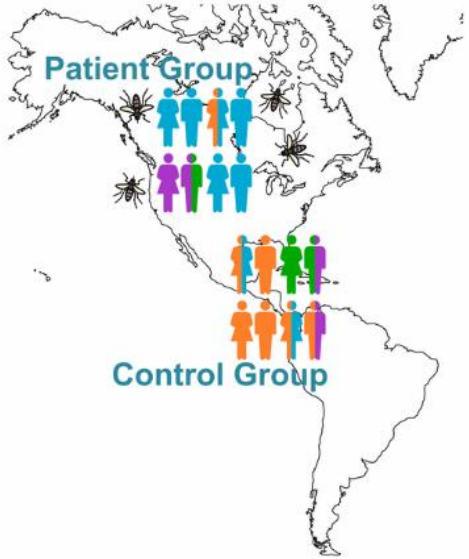
Local adaptation in Africa driven by a flavivirus



Migration of African and European parental populations ~500 years ago



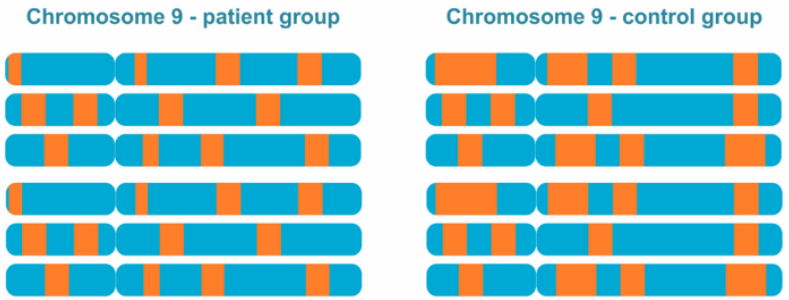
Admixed descendants have differential resistance to dengue disease

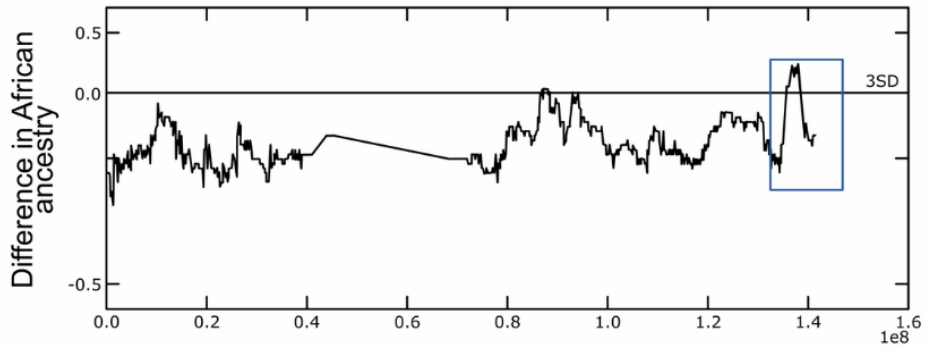


Possible motors of positive selection in Africa:

- **Yellow fever virus**
- Dengue fever virus
- Zika virus

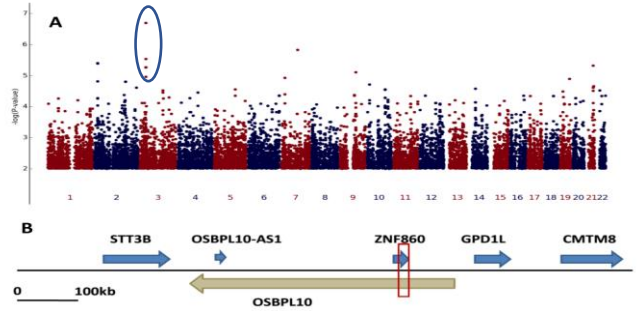
Admixture mapping





***RXRA* - Retinoid X Receptor Alpha**

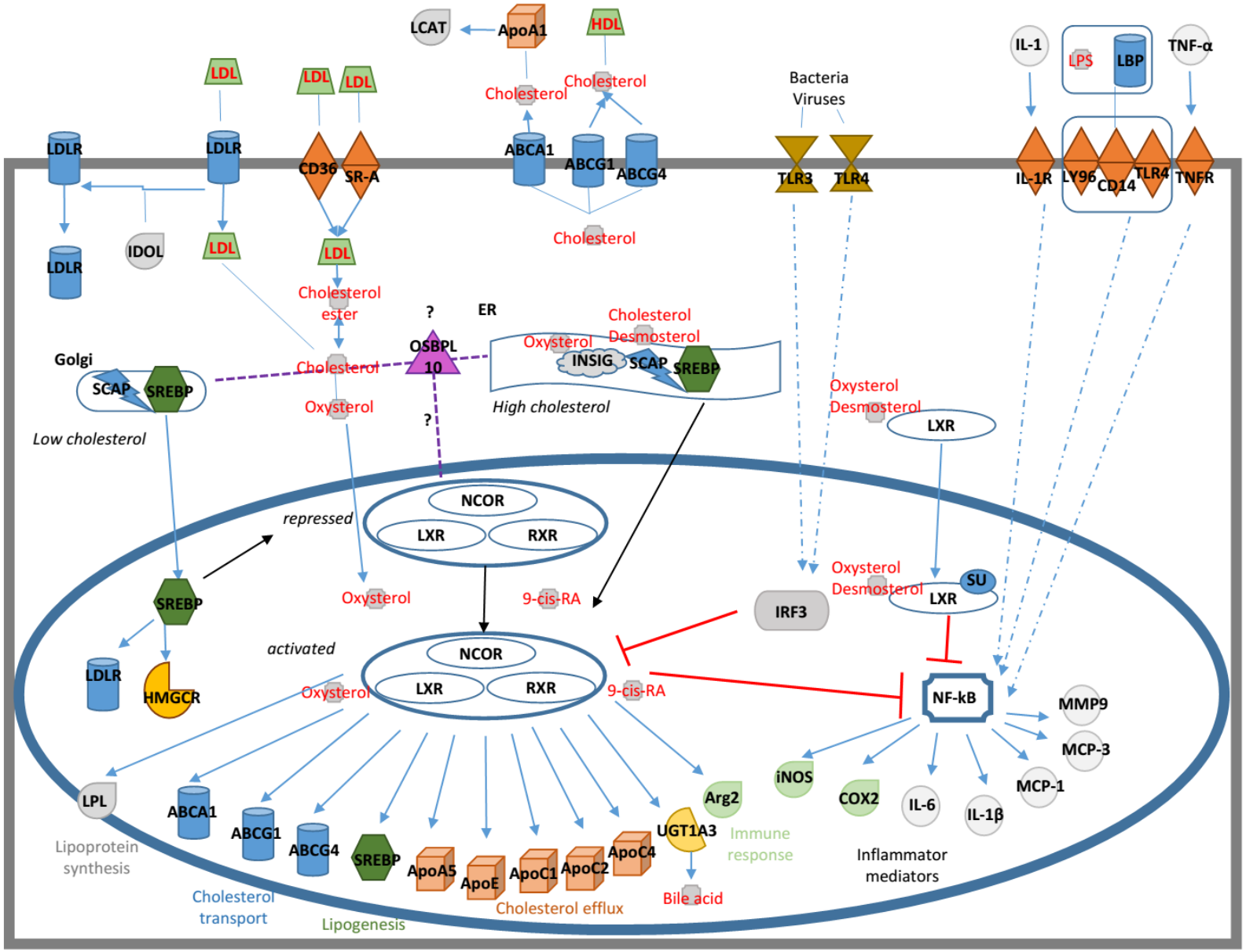
Ancestry fine-matched GWAS



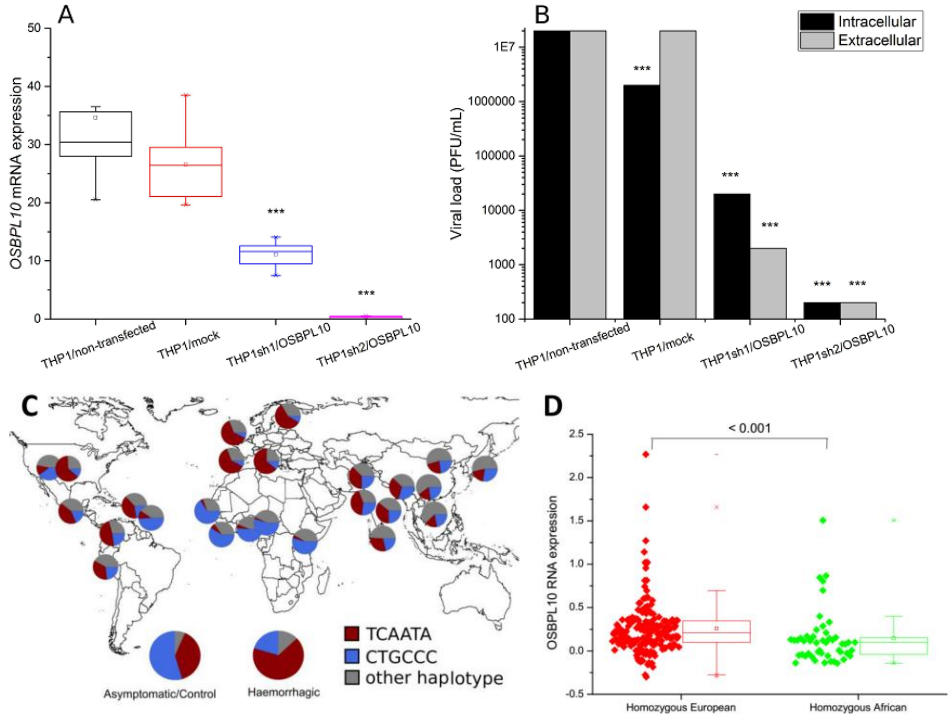
***OSBPL10* - oxysterol binding protein-like 10**

LXR/RXR activation pathway in hepatocytes and macrophages

Integrates lipid metabolism and immune functions: virus entrance/replication and cytokine production



Functional assay: *OSBPL10* knockdown decreases DENV replication



INSTITUTO
DE INVESTIGAÇÃO
E INOVAÇÃO
EM SAÚDE
UNIVERSIDADE
DO PORTO

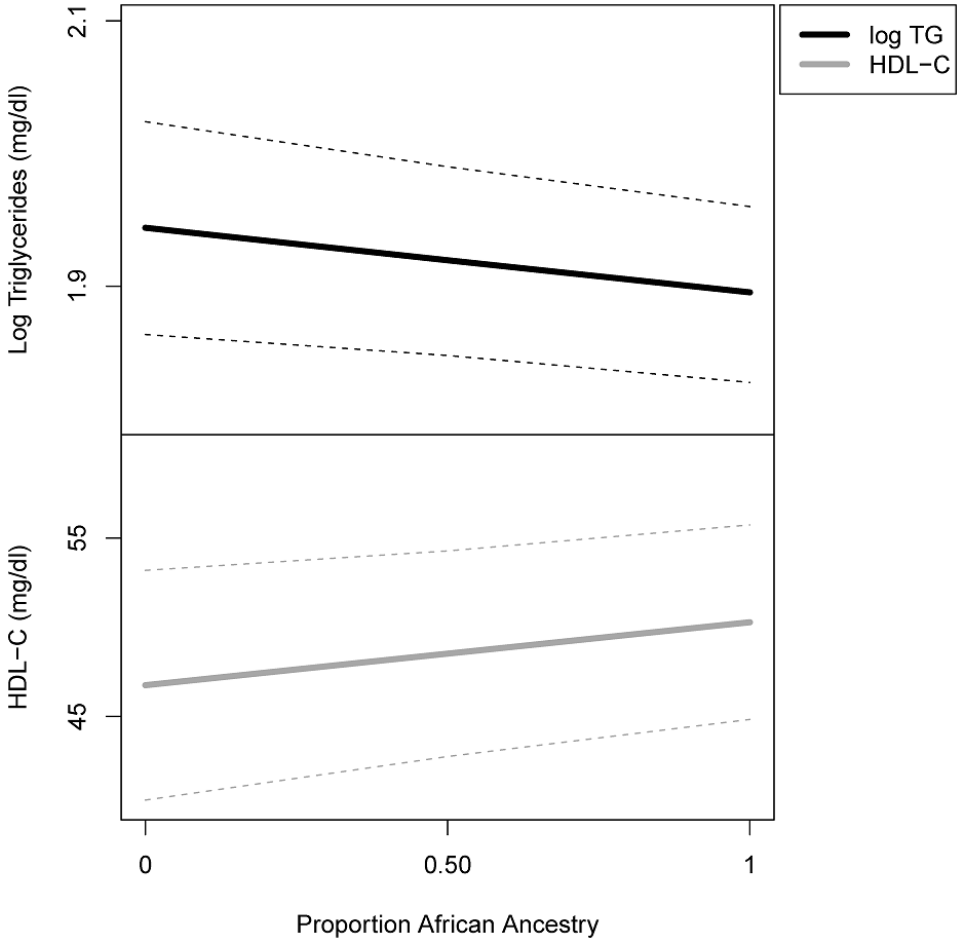
EXPERT REVIEWS

Interethnic variation in lipid profiles: implications for underidentification of African–Americans at risk for metabolic disorders

Expert Rev. Endocrinol. Metab. 7(6), 659–667 (2012)

Amy R Bentley and Charles N Rotimi*

Interethnic differences exist in the distribution of serum lipids, with African–Americans (AAs) generally having a healthier lipid profile than other US ethnic groups. Similar lipid distributions



Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

Lovastatin for the Treatment of Adult Patients With Dengue: A Randomized, Double-Blind, Placebo-Controlled Trial

James Whitehorn,[1,2,a] Chau Van Vinh Nguyen,[3,a] Lam Phung Khanh,[2] Duong Thi Hue Kien,[2] Nguyen Than Ha Quyen,[2] Nguyen Thi Thanh Tran,[2] Nguyen Thuy Hang,[2] Nguyen Thanh Truong,[3] Luong Thi Hue Tai,[3] Nguyen Thi Cam Huong,[3] Vo Thanh Nhon,[4] Ta Van Tram,[4] Jeremy Farrar,[2,5] Marcel Wolbers,[2,5] Cameron P. Simmons,[2,5,6,a] and Bridget Wills[2,5,a]

Conclusions. We found lovastatin to be safe and well tolerated in adults with dengue. However, although the study was not powered to address efficacy, we found no evidence of a beneficial effect on any of the clinical manifestations or on dengue viremia. Continuing established statin therapy in patients who develop dengue is safe.

Our current investigation related with dengue fever:

Test several lipid metabolism-interfering drugs in dengue infection assays

INSTITUTO DE INVESTIGAÇÃO E INOVAÇÃO EM SAÚDE
UNIVERSIDADE DO PORTO

Protective genes can differ but be related amongst population groups

OSBPL10* and *RXRA

Cuban

LXR/RXR activation pathway
Lipid metabolism and
cytokine/chemokine production
hepatocytes and macrophages

CHST10, AHRR, GRIP1* and *PPP2R5E

Thai

Xenobiotic metabolism pathway
PXR/CAR-RXRA
Xenobiotic metabolism and
inflammatory response

Unifying framework for several genes potentially protective against dengue

VDR

Vietnamese

VDR/RXR activation pathway
Immune function, sterol metabolism,
cell growth and proliferation

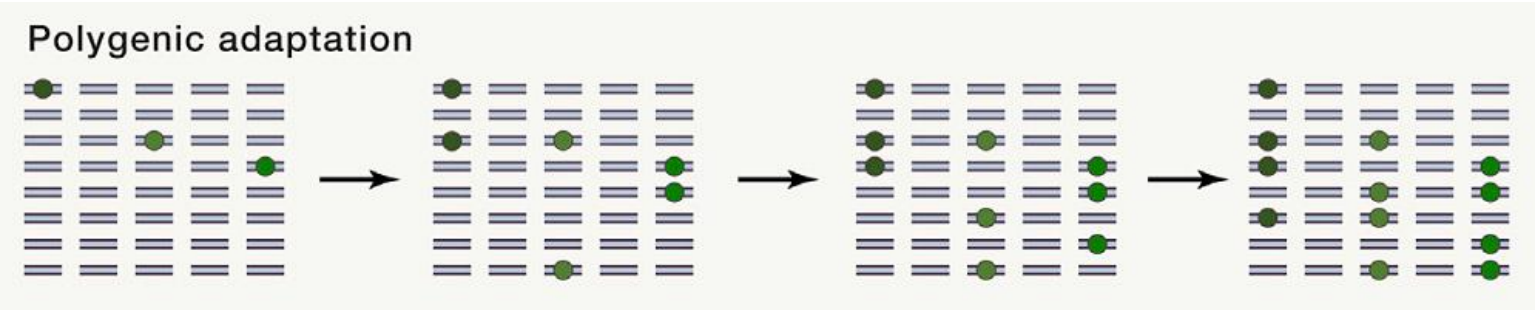
PLCE1

Vietnamese

PLCB4

Thai

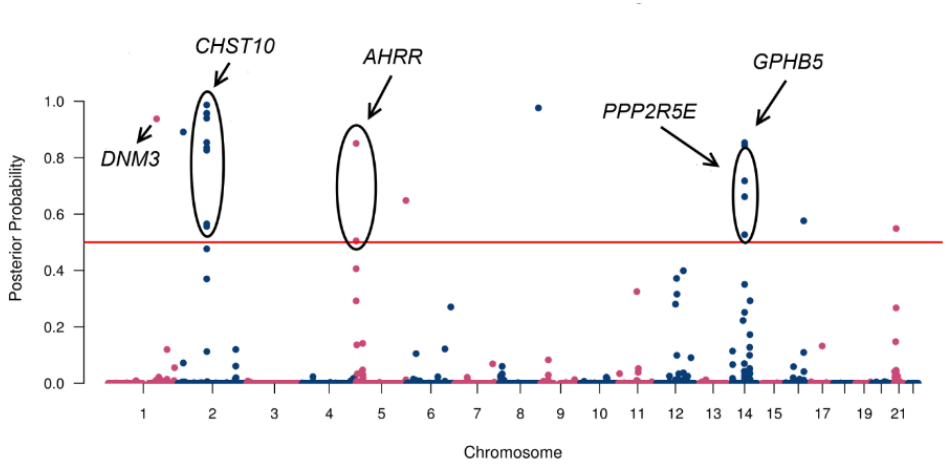
PPARA/RXRA activation pathway
Lipid metabolism and acute
phase inflammation response



PLOS NEGLECTED TROPICAL DISEASES

Joint ancestry and association test indicate two distinct pathogenic pathways involved in classical dengue fever and dengue shock syndrome

Marisa Oliveira[1,2,3,4], Worachart Lert-itthiporn[5], Bruno Cavadas[1,2,3], Verónica Fernandes[1,2], Ampaiwan Chuansumrit[6], Orlando Anunciação[2], Isabelle Casademont[4,7], Fanny Koeth[4,7], Marina Penova[4,7,8], Kanchana Tangnararatchakit[6], Chiea Chuen Khor[9,10], Richard Paul[4,7,11], Prida Malasit[12,13], Fumihiko Matsuda[7,8], Etienne Simon-Lorière[4,7,11], Prapat Suriyaphol[5], Luisa Pereira[1,2,14‡*], Anavaj Sakuntabhai[4,7,11‡*]



Xenobiotic metabolism pathway

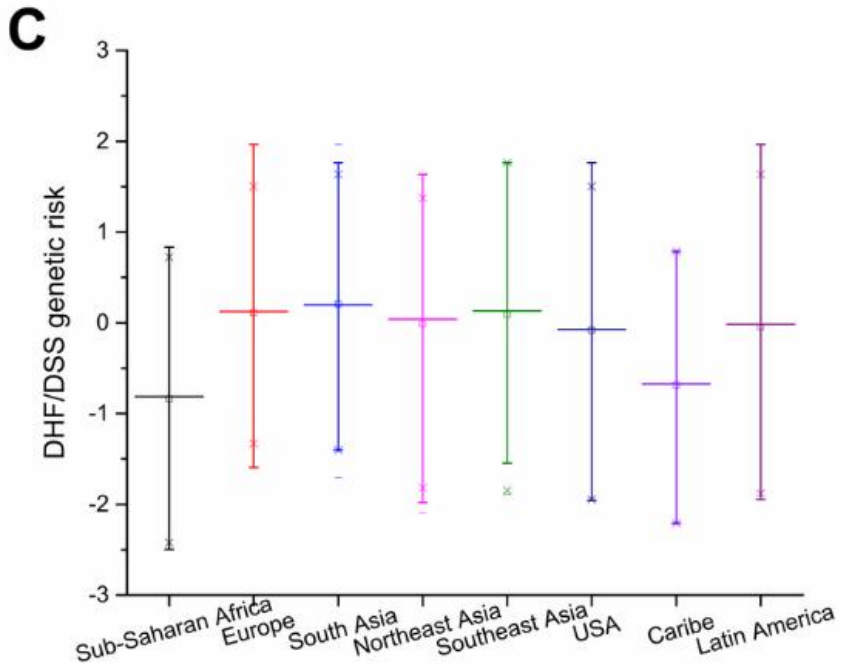
INSTITUTO DE INVESTIGAÇÃO E INOVAÇÃO EM SAÚDE
UNIVERSIDADE DO PORTO

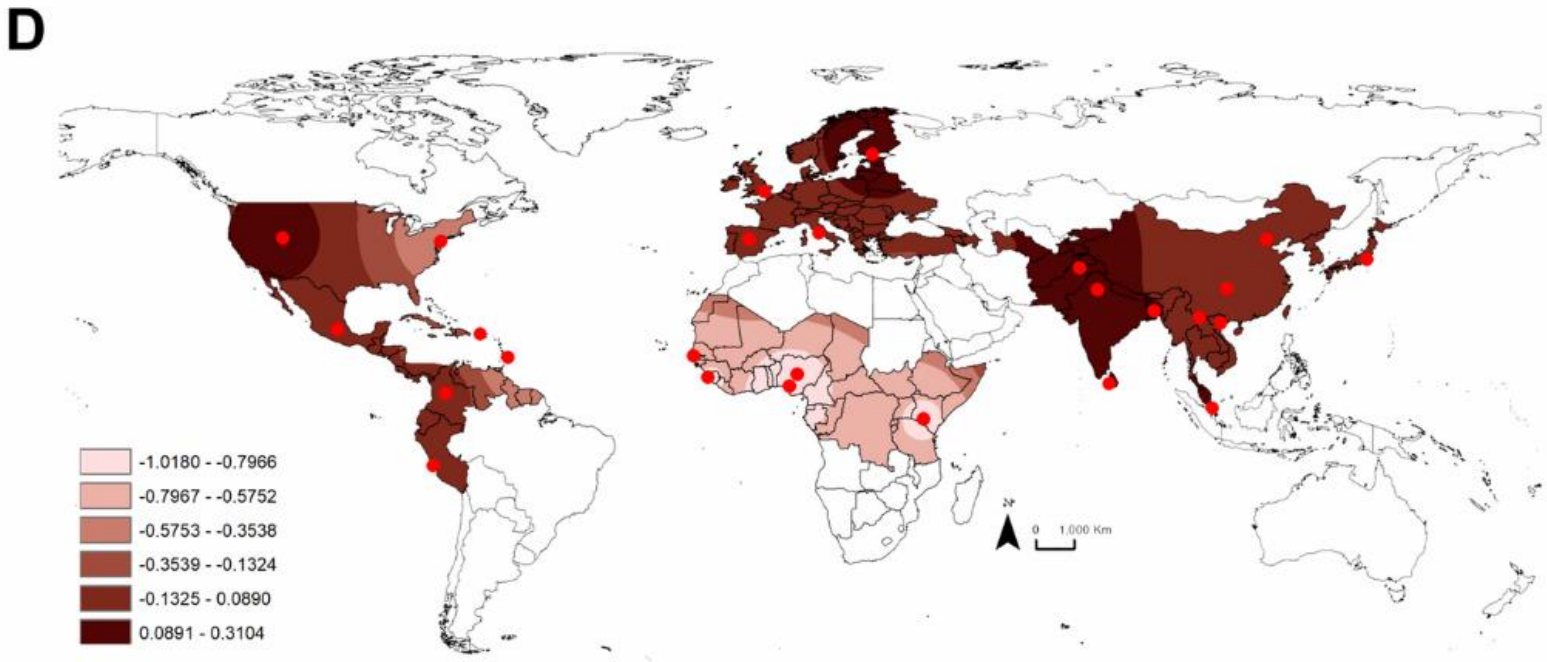
Genetic risk to DHF/DSS phenotypes of dengue disease

Future VIROLOGY

Host ancestry and dengue fever: from mapping of candidate genes to prediction of worldwide genetic risk

Marisa Oliveira[1,2,3,4], Joana Ferreira[1,2,3], Verónica Fernandes[1,2], Anavaj Sakuntabhai[4,5,6] & Luisa Pereira*[,1,2,7]



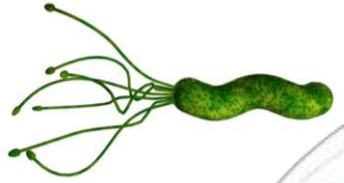


INSTITUTO
DE INVESTIGAÇÃO
E INOVAÇÃO
EM SAÚDE
UNIVERSIDADE
DO PORTO

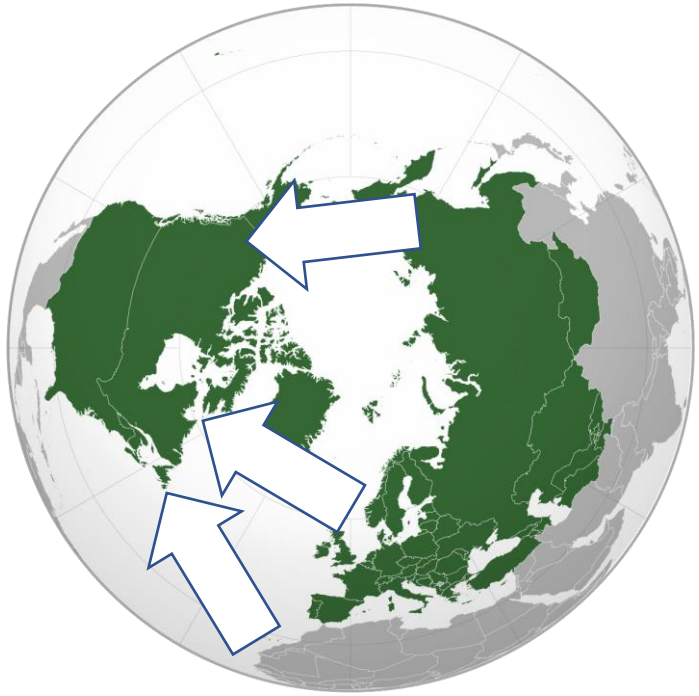
Old pathogen-human interaction – *Helicobacter pylori* – *in vitro* evaluation of coevolution

More time for coevolution in Africa
Lower virulence of African strains
Africans better naturally protected

“African enigma”



Dual population structure
Bottlenecks
Disrupted coevolution – maladaptation – new adaptation
Potential increased virulence
Asians and Europeans worse protected



Encounter of mismatched host-pathogen groups
Disrupted coevolution

Old HIR – *Helicobacter pylori* – infection assays and AmpliSeq

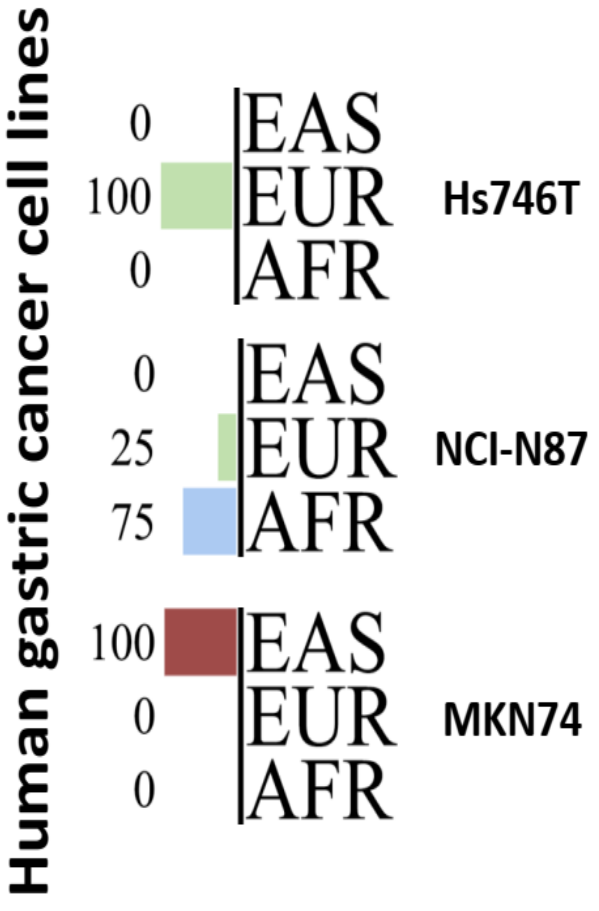
microorganisms

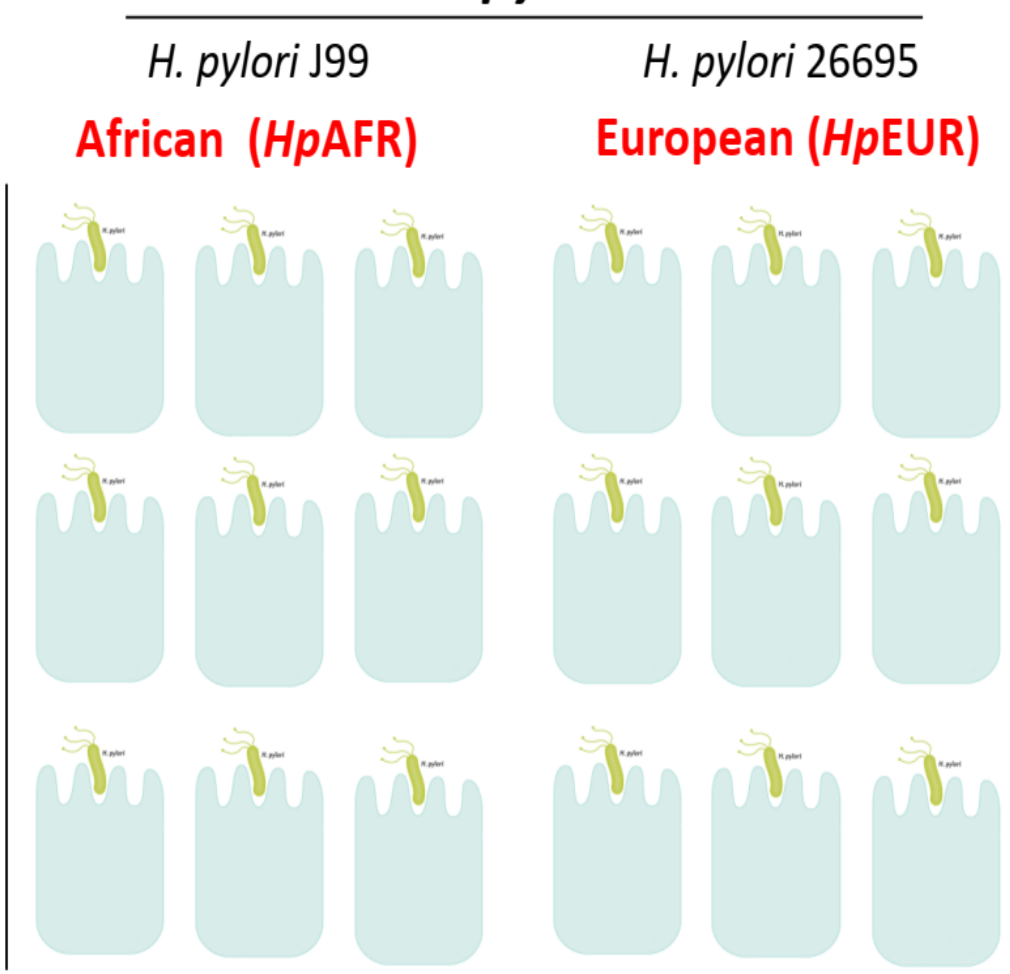
MDPI

Article

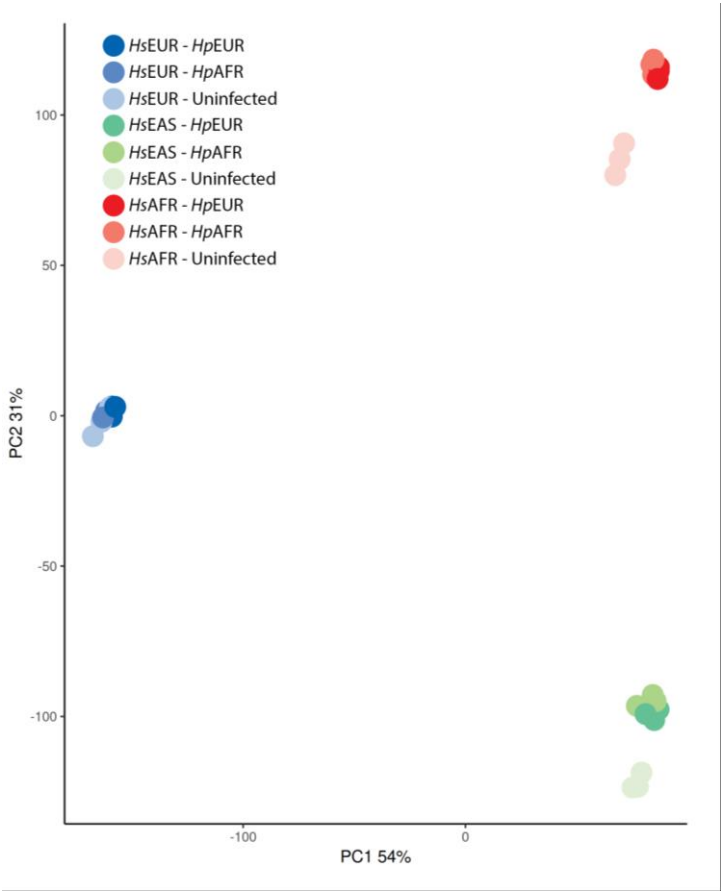
Shedding Light on the African Enigma: In Vitro Testing of *Homo sapiens-Helicobacter pylori* Coevolution

Bruno Cavadas [1,2,3,*], Marina Leite [1,2,4], Nicole Pedro [1,2,3], Ana C. Magalhães [1,2,3], Joana Melo [1,2,3], Marcelo Correia [1,2], Valdemar Máximo [1,2,4], Rui Camacho [5,6], Nuno A. Fonseca [7], Ceu Figueiredo [1,2,4] and Luísa Pereira [1,2,4]

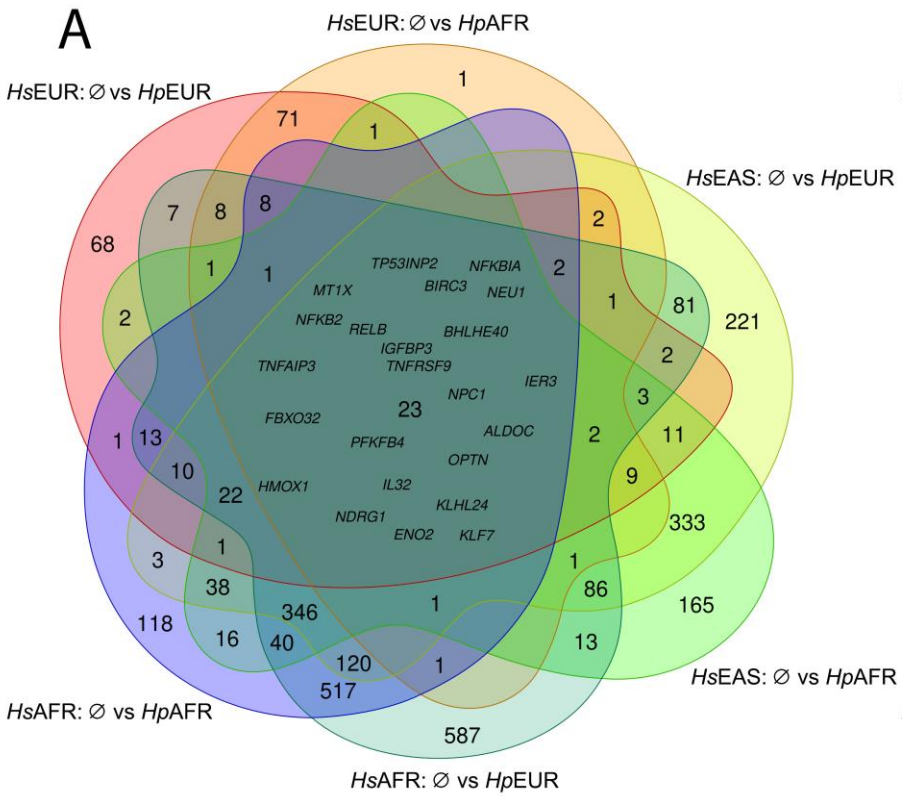




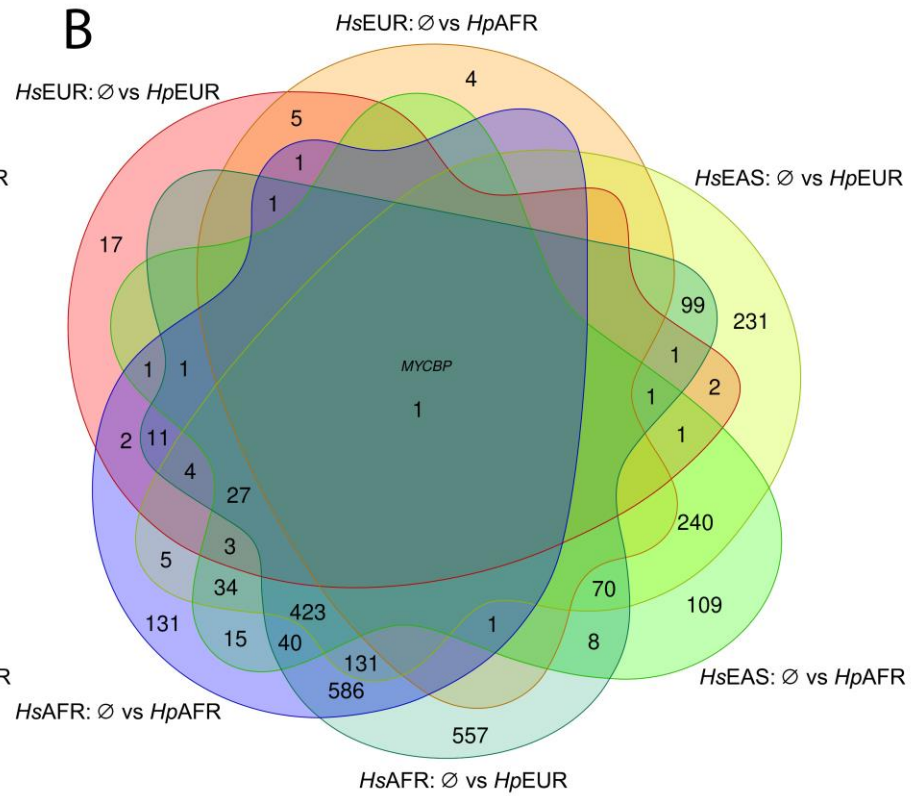
Old HIR – *Helicobacter pylori* – genome-wide transcriptomics



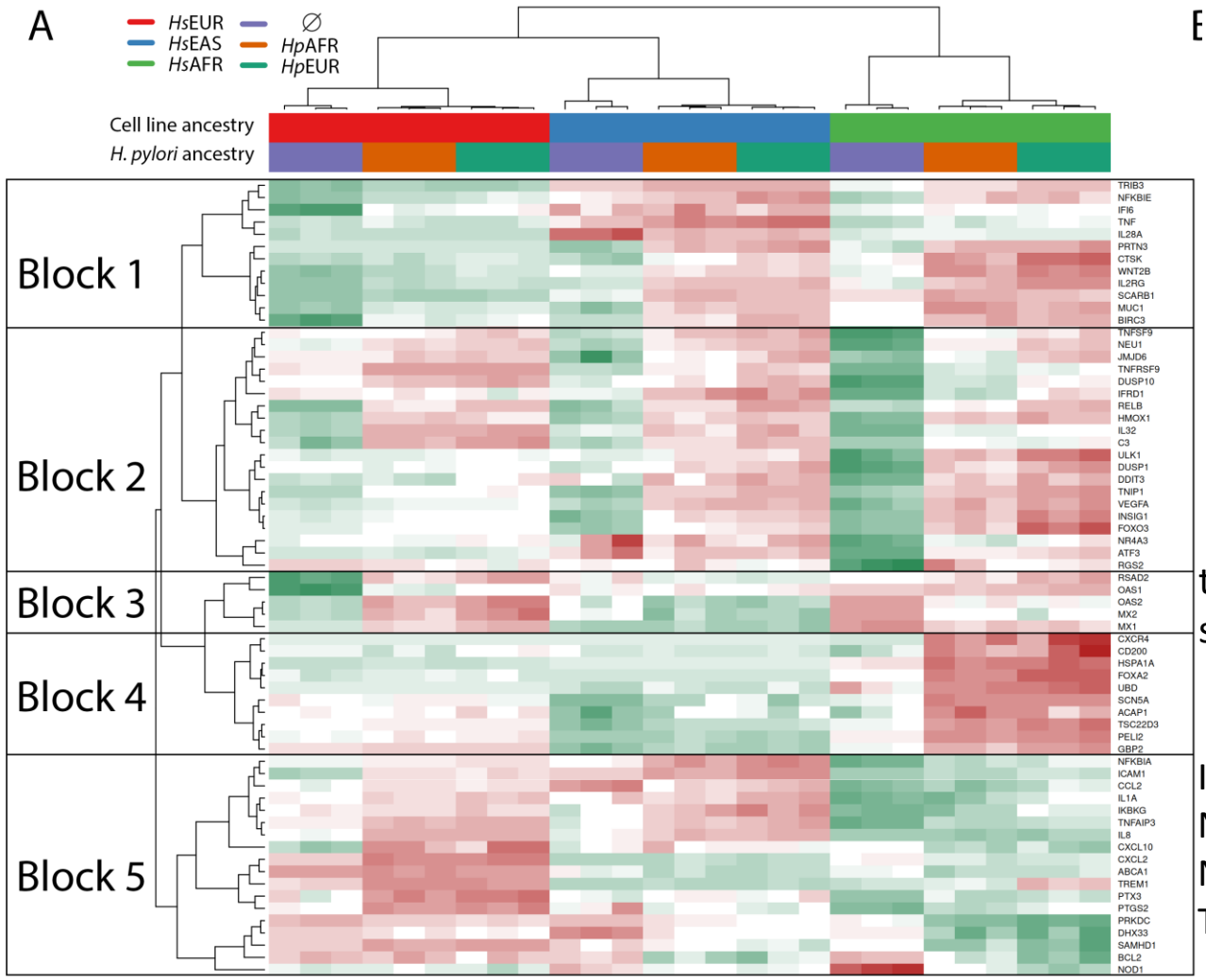
Up-regulation



Down-regulation



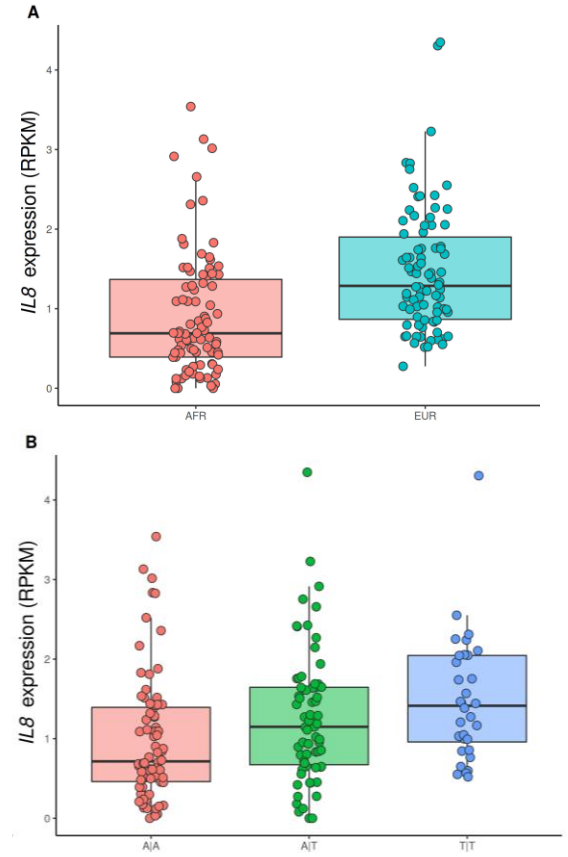
Old HIR – *Helicobacter pylori* – innate immune response

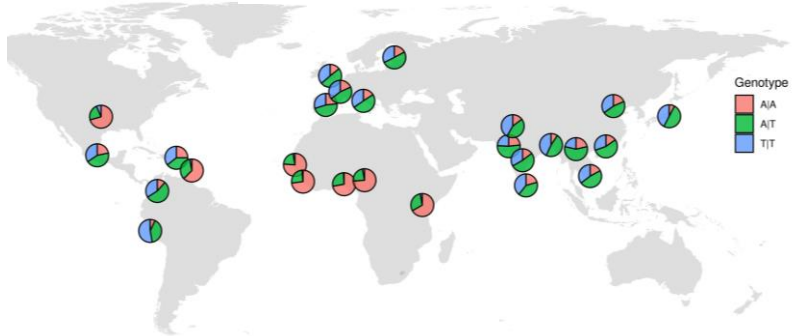


type-1 interferon signaling pathway

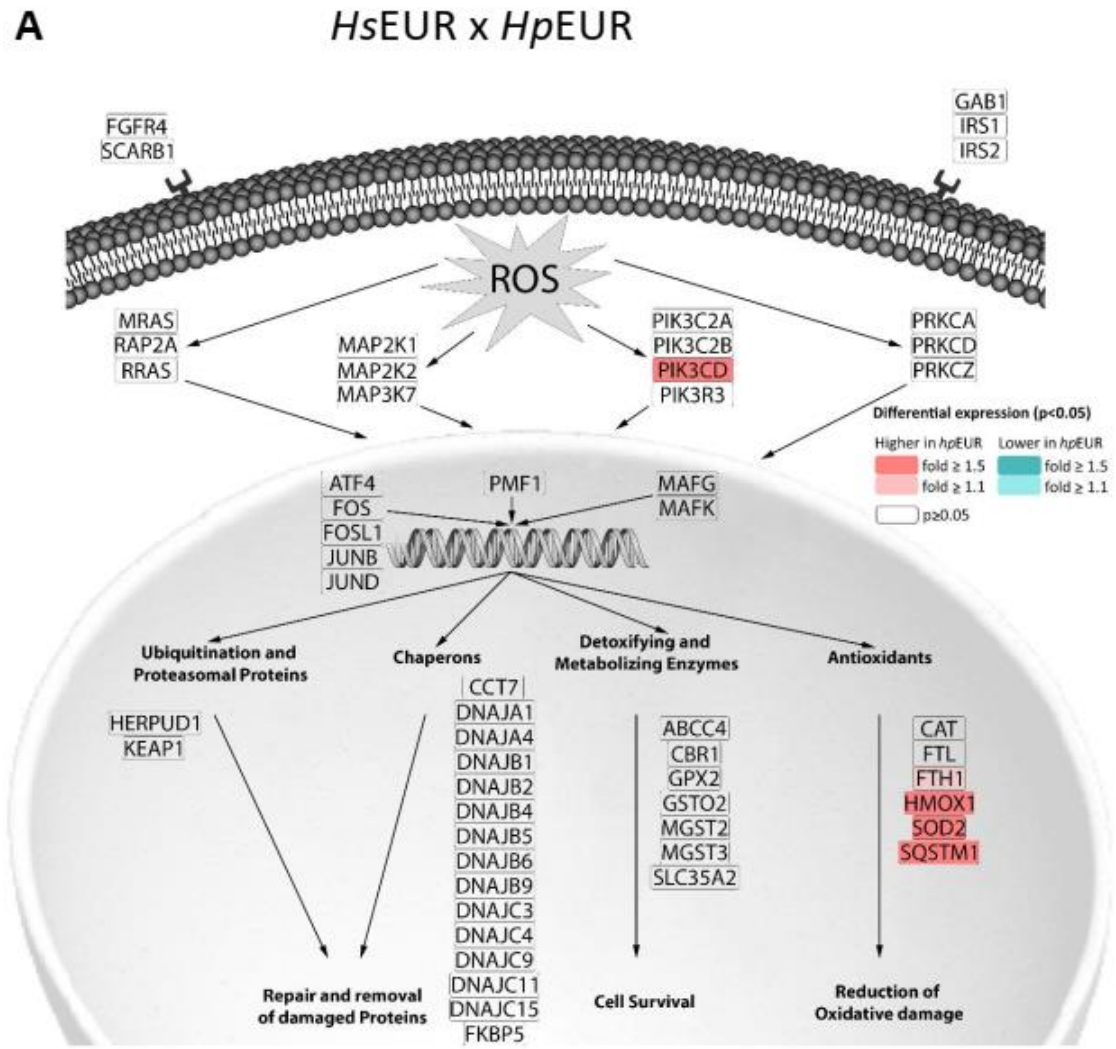
IL-17 s p
NF-kappa B s p
NOD-like receptor s p
TNF s p

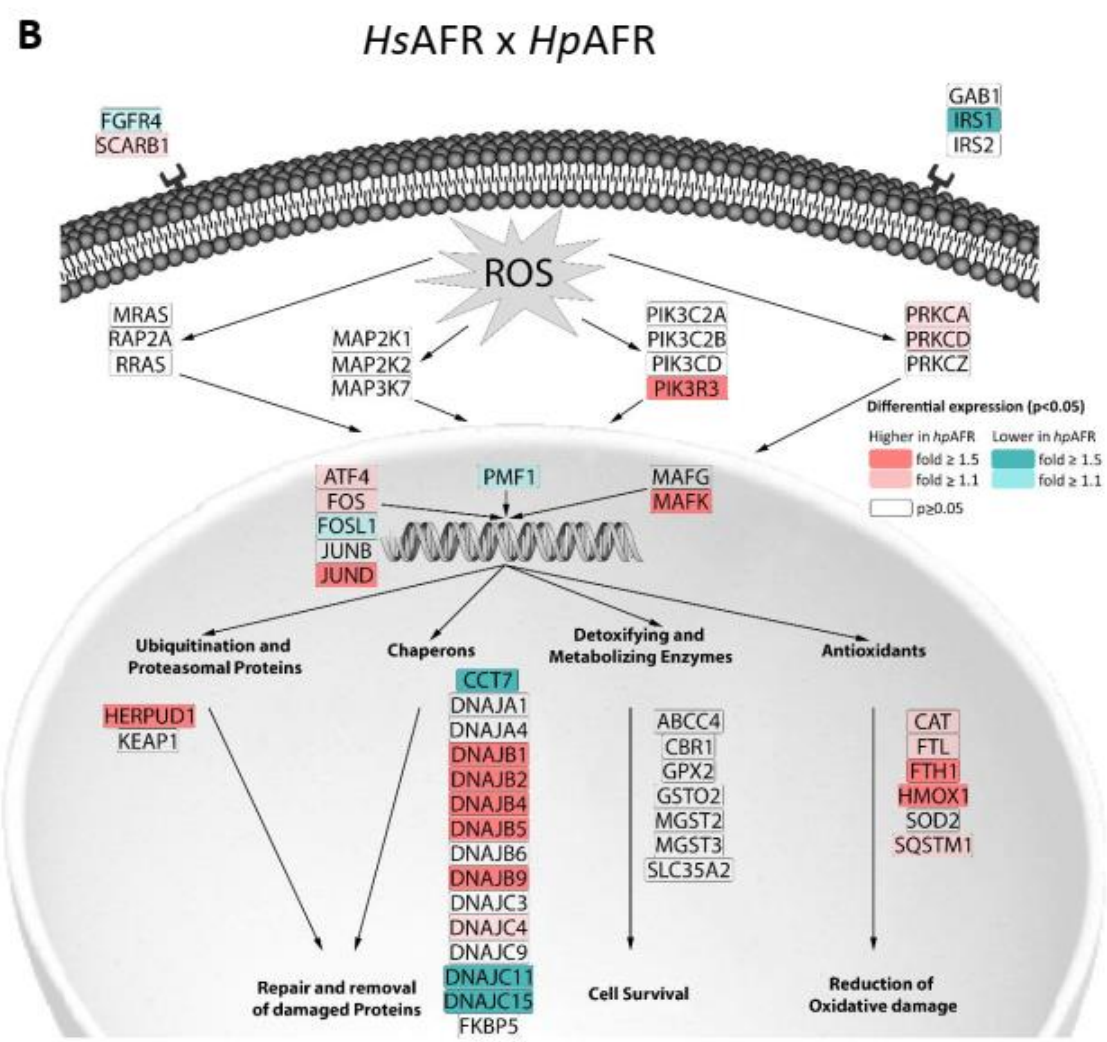
inflammation





Old HIR – *Helicobacter pylori* – oxidative stress





Old HIR – *Helicobacter pylori* – Coevolution – main conclusions

(1) host response to *H. pylori* was greatly molded by human ancestry

(2) African human ancestry showed clear signs of coevolution with *H. pylori* – broader and better adapted molecular response

(3) European human ancestry was maladapted – mainly activation of the immune system

(4) Asian ancestry in between (but closer to the coevolved African)

(5) mismatched host-bacterium ancestry did not appear to be an important differentiator of gene expression, at least at the initial stages of infection, as we analyzed here

INSTITUTO
DE INVESTIGAÇÃO
E INOVAÇÃO
EM SAÚDE
UNIVERSIDADE
DO PORTO