Gene-Culture Coevolution: Adult Lactose Tolerance in Africa

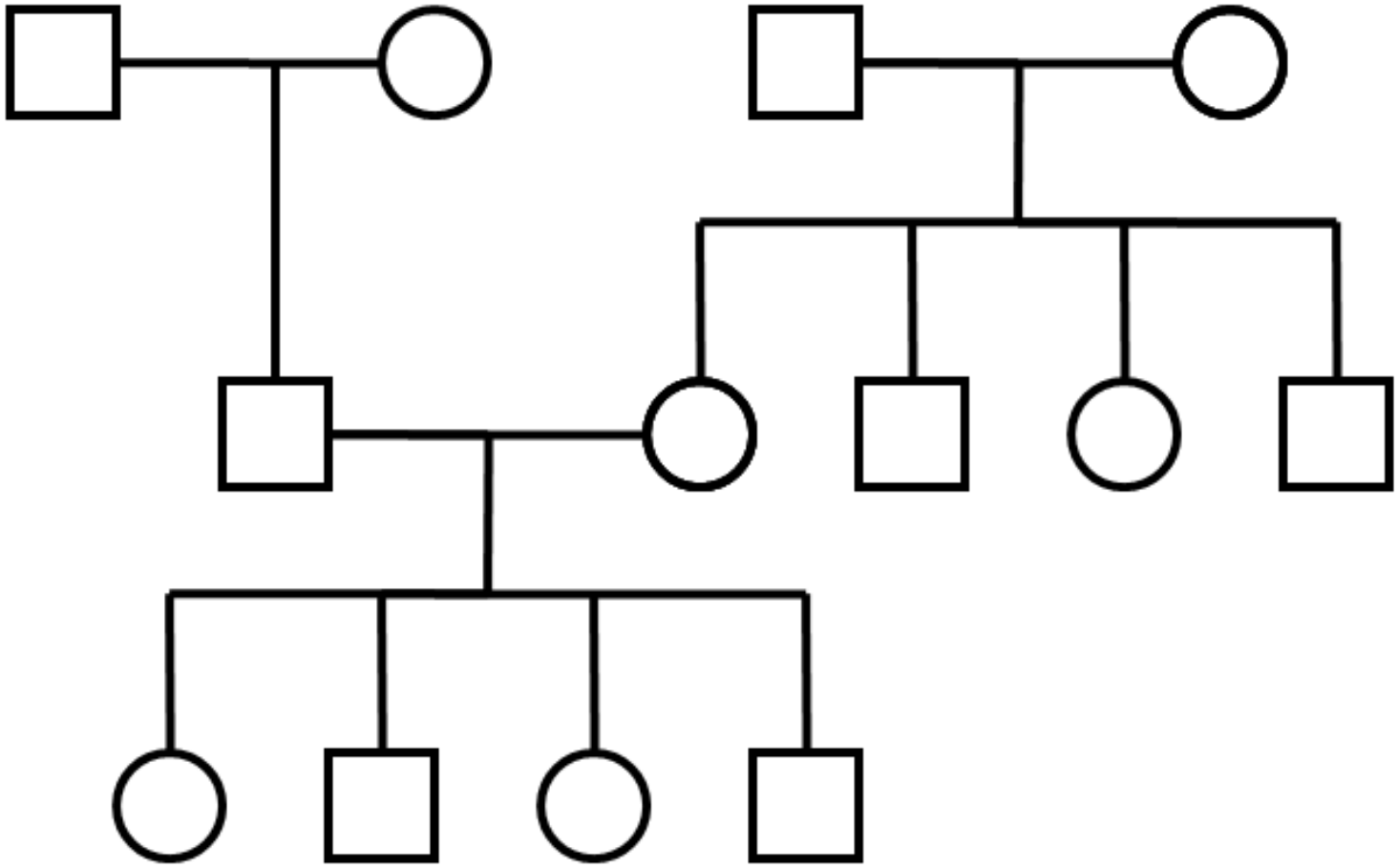
Floyd A. Reed

Max Planck Institute for Evolutionary Biology,
Plön, Germany

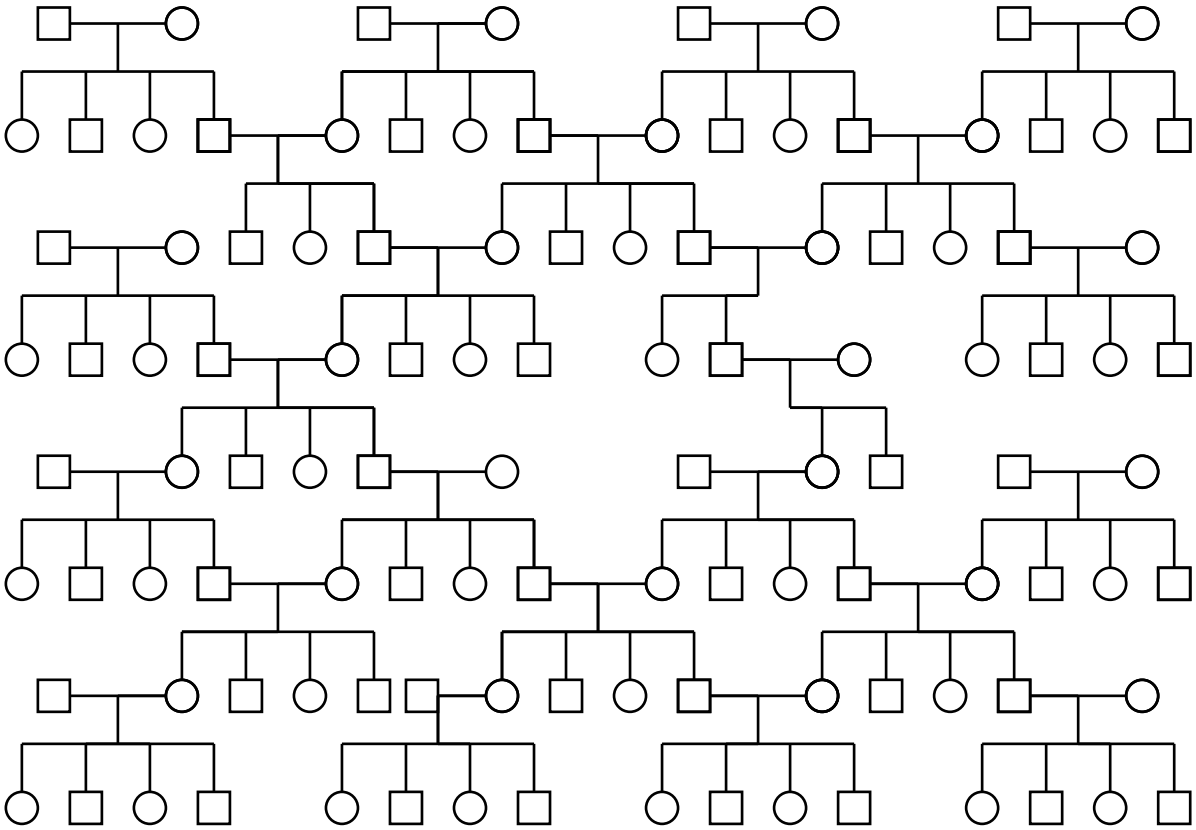
MAX-PLANCK-GESELLSCHAFT

First: an overview of population/evolutionary genetics and human genetic variation

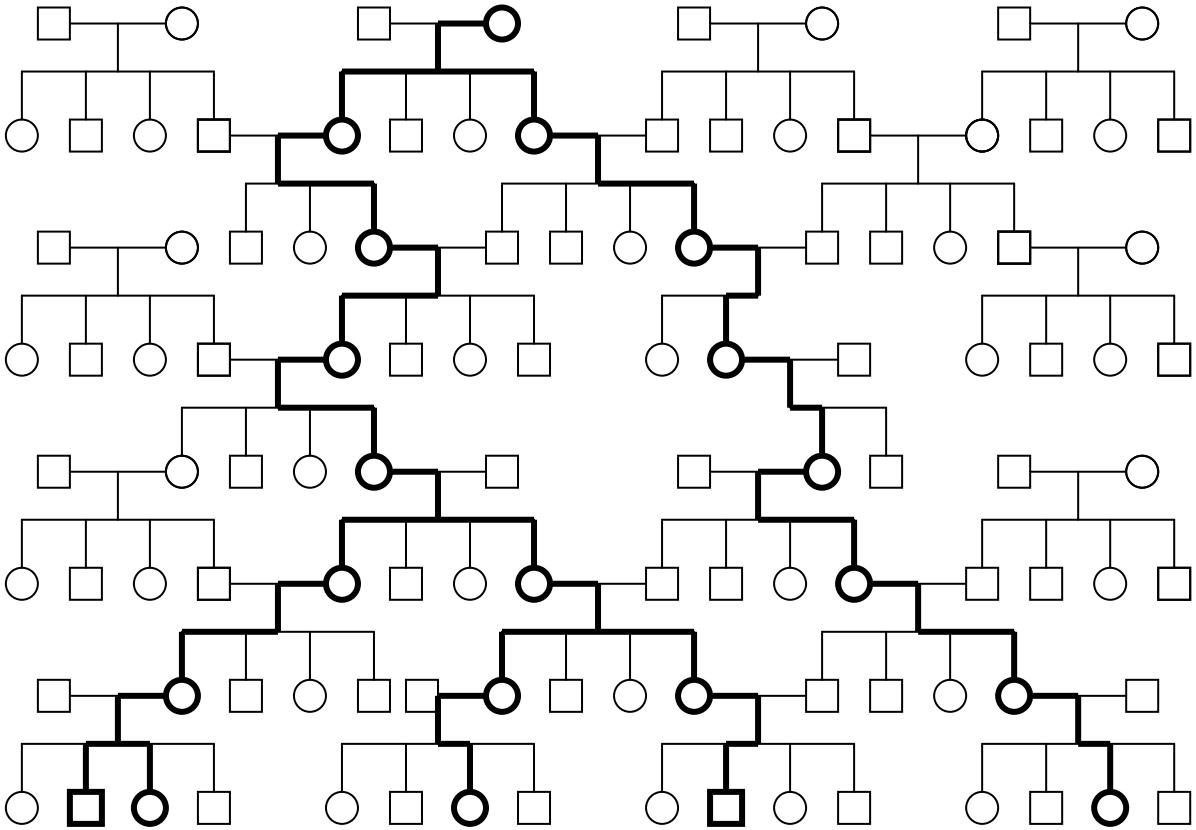
A family pedigree



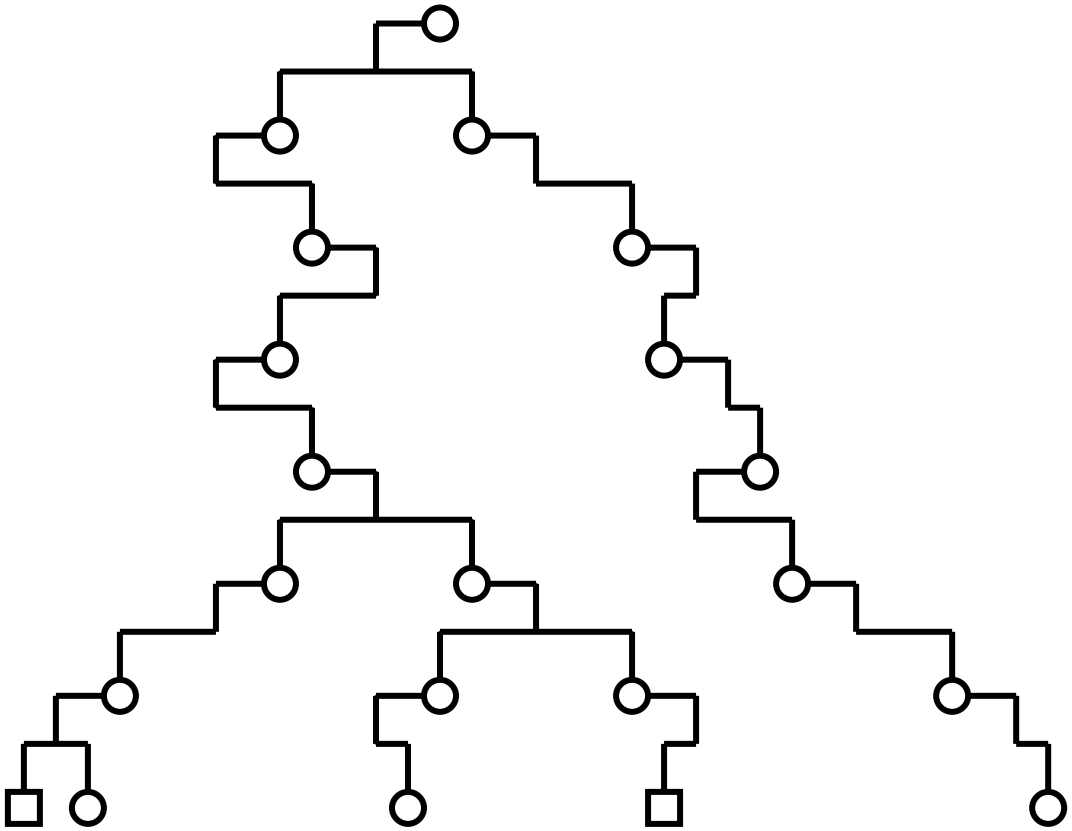
Moving from pedigrees to populations



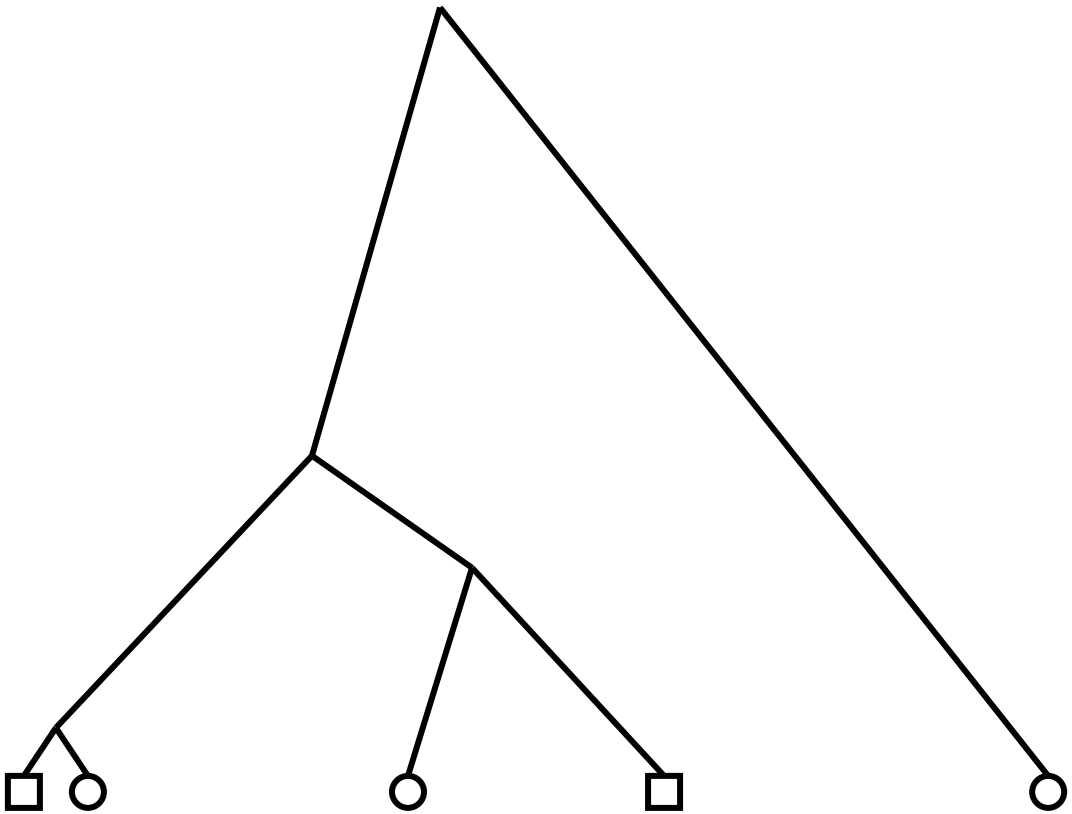
Maternal inheritance, mitochondrial DNA



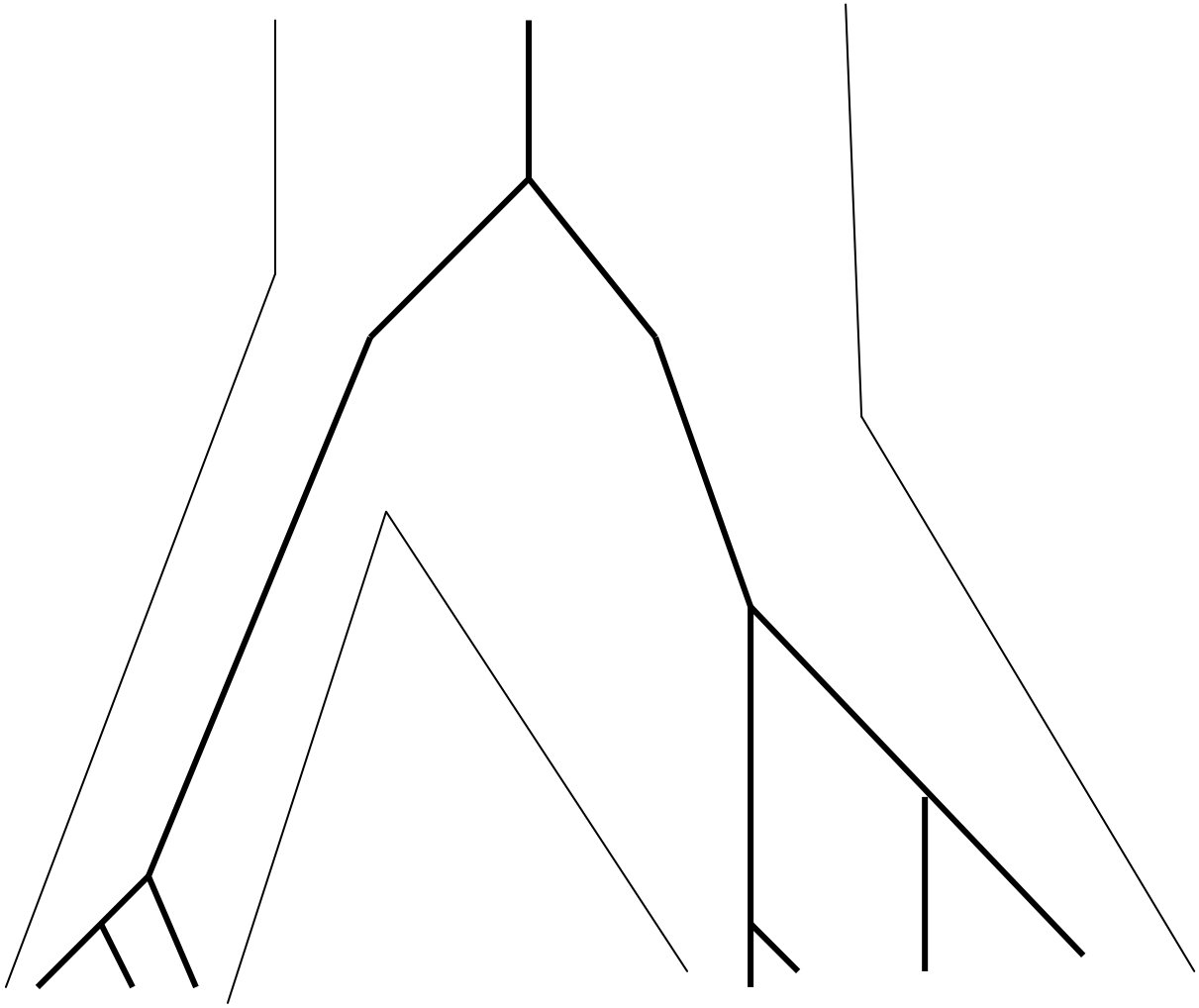
Moving from populations to lineages



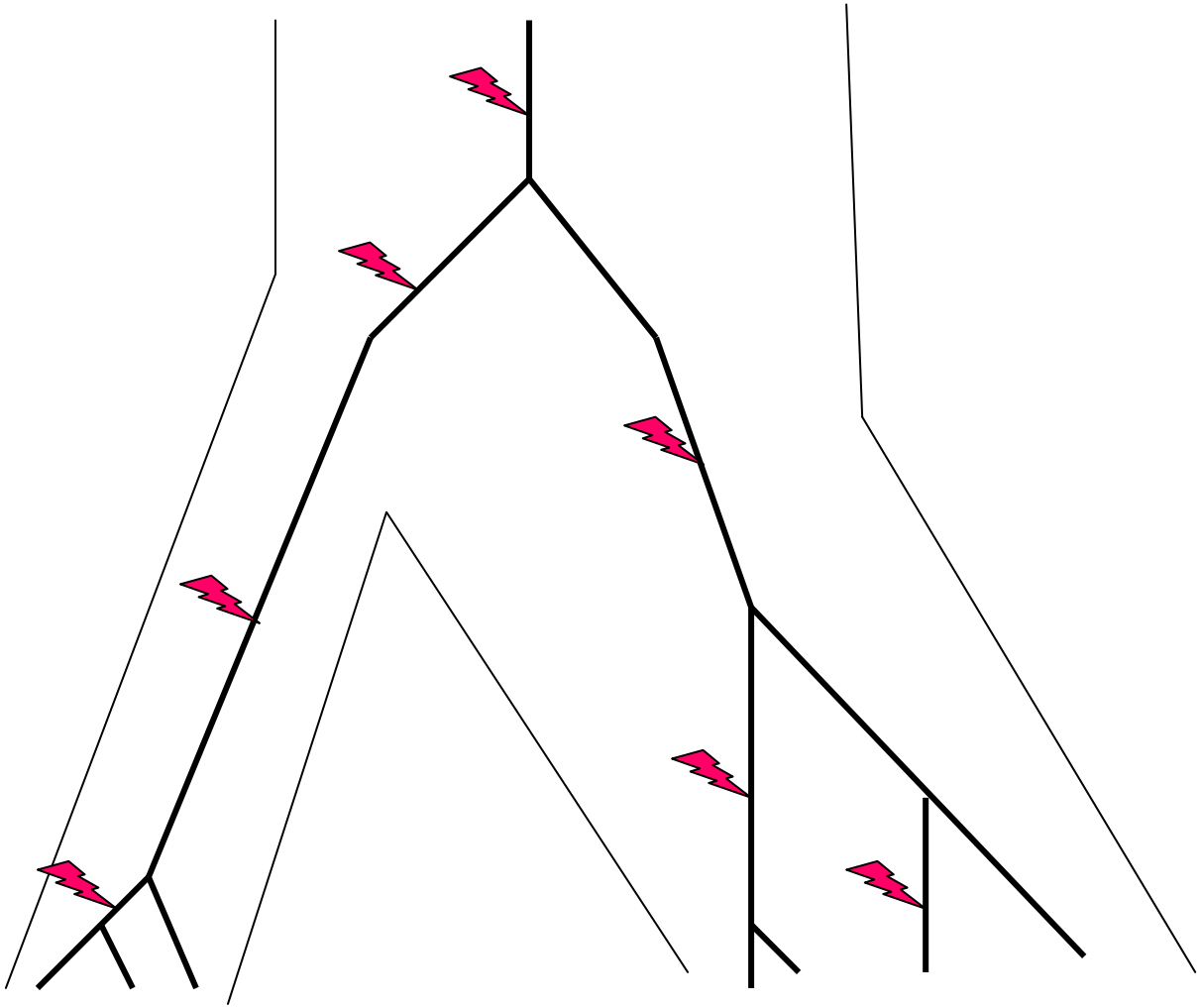
Genetic lineages from sampled individuals



Moving from populations to species



Mutations occur over time



But we don’t have trees we only have modern DNA samples

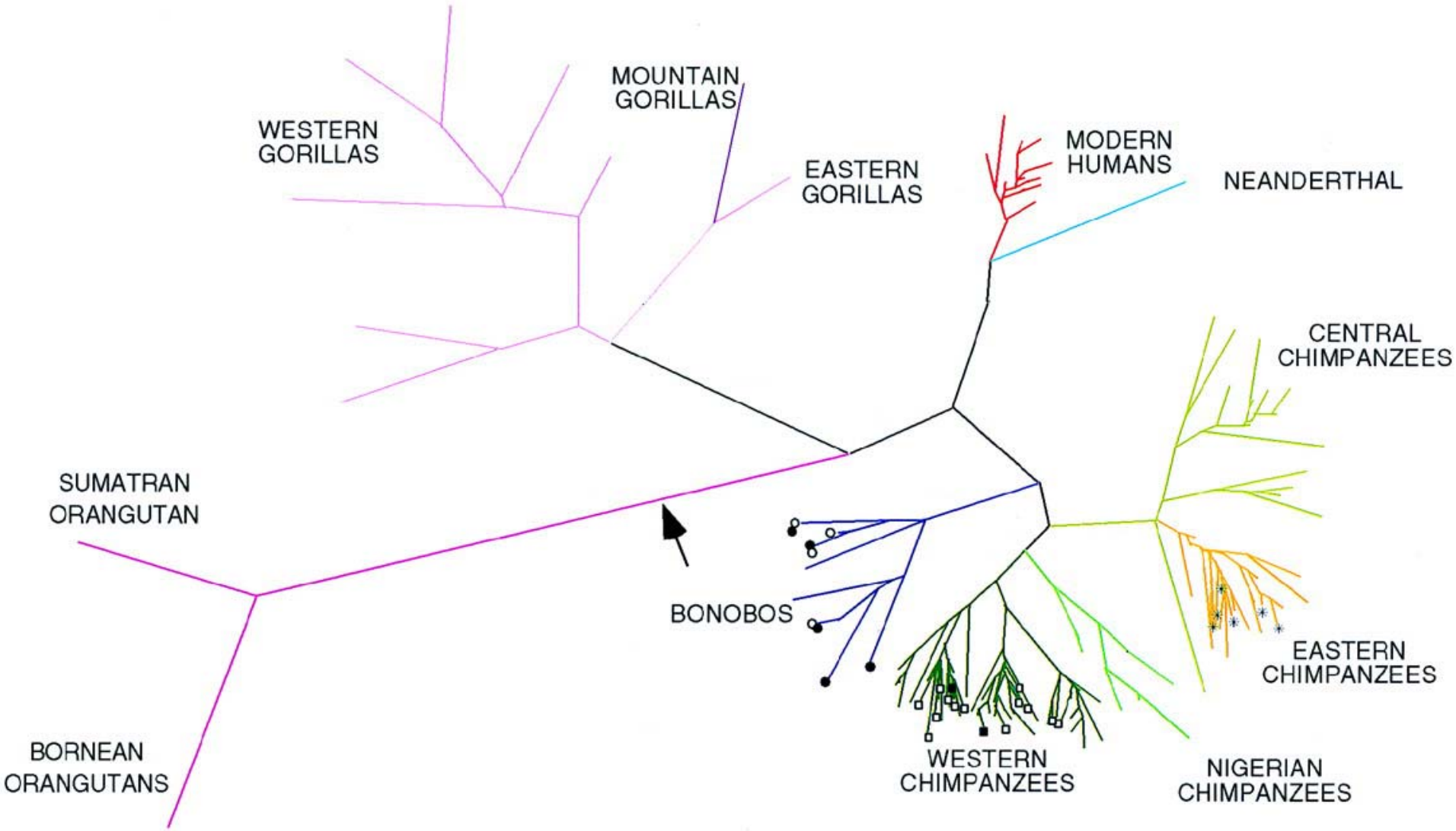
Sample A

AATACGCGGATTGCTCAACTACCCGATC
AATACGCGGATTGCTCAACTACCCGATC
AATACGCGGATTGCTCAACTACCCGGTC

Sample B

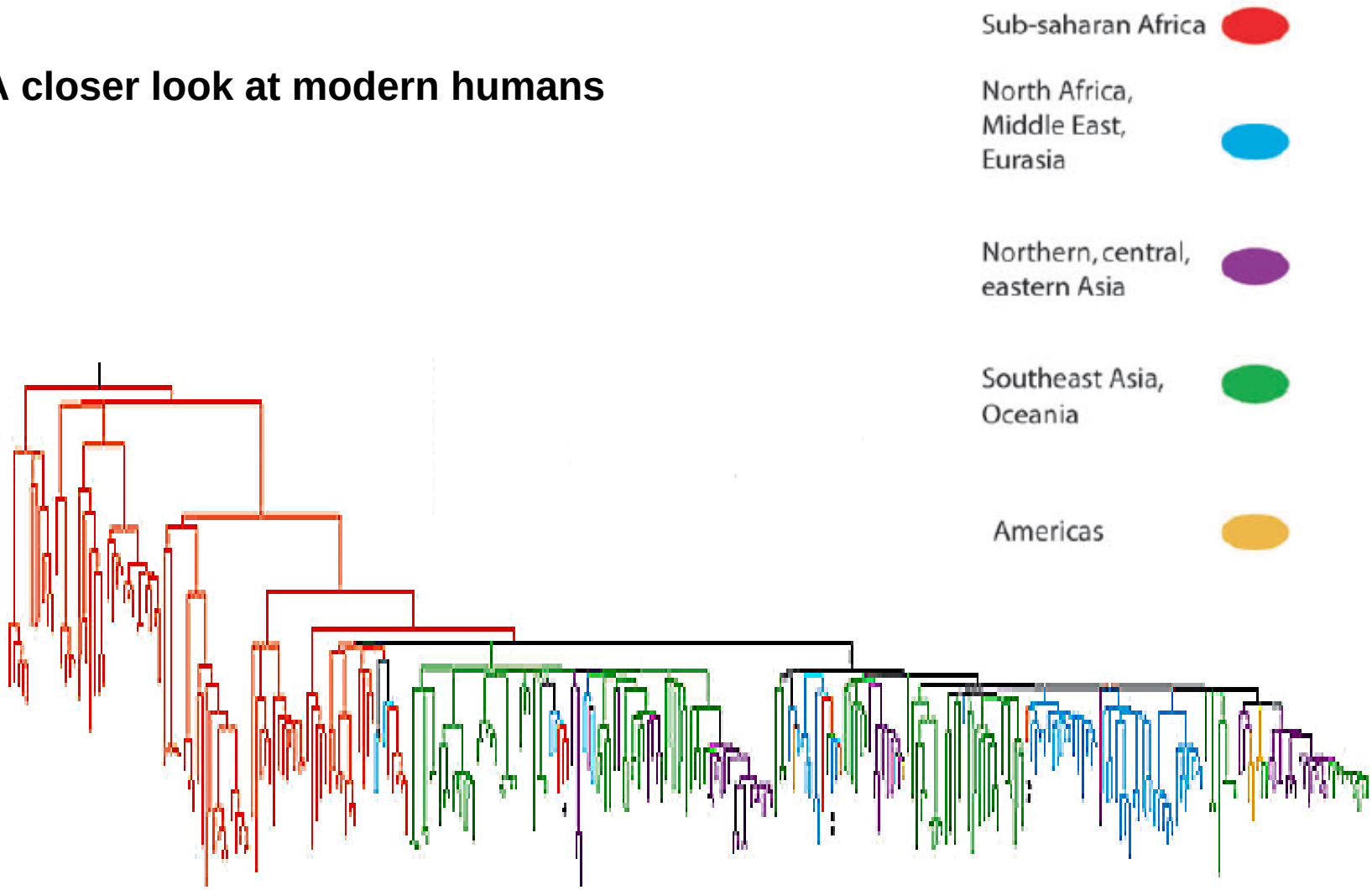
AATACGCGTAATGCTCAGCTACTCGATC
AATCCGCGTAATGCTCAGCTACCCGATC
AATCCGCGTAATGCTCAGCTACCCGATC

The big picture: modern humans are very similar to each other



Gagneux et al. 1999 PNAS 96:5077

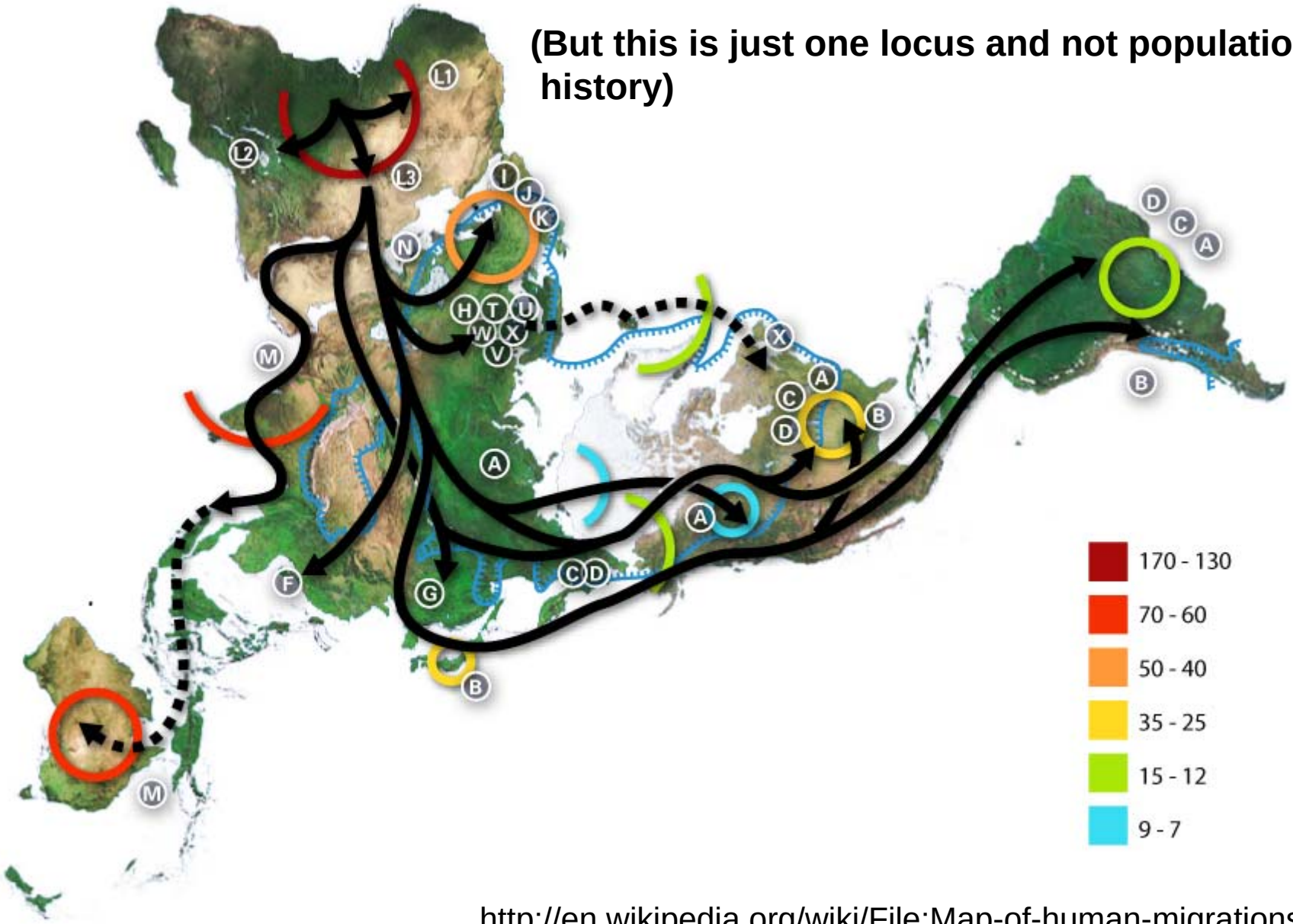
A closer look at modern humans



Gonder et al. 2007 MBE 24:757

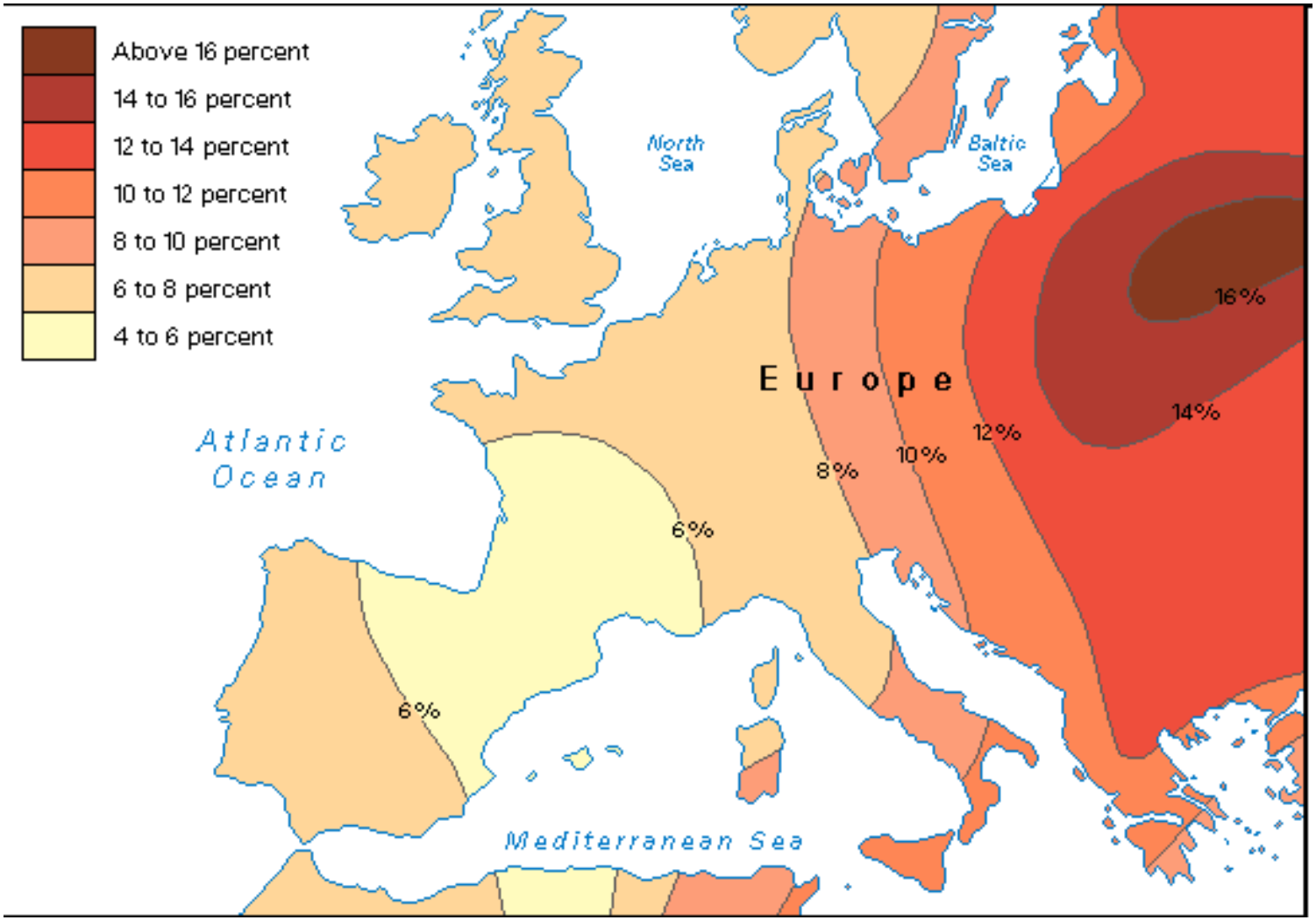
Maternal Lineage Migration Map of the World

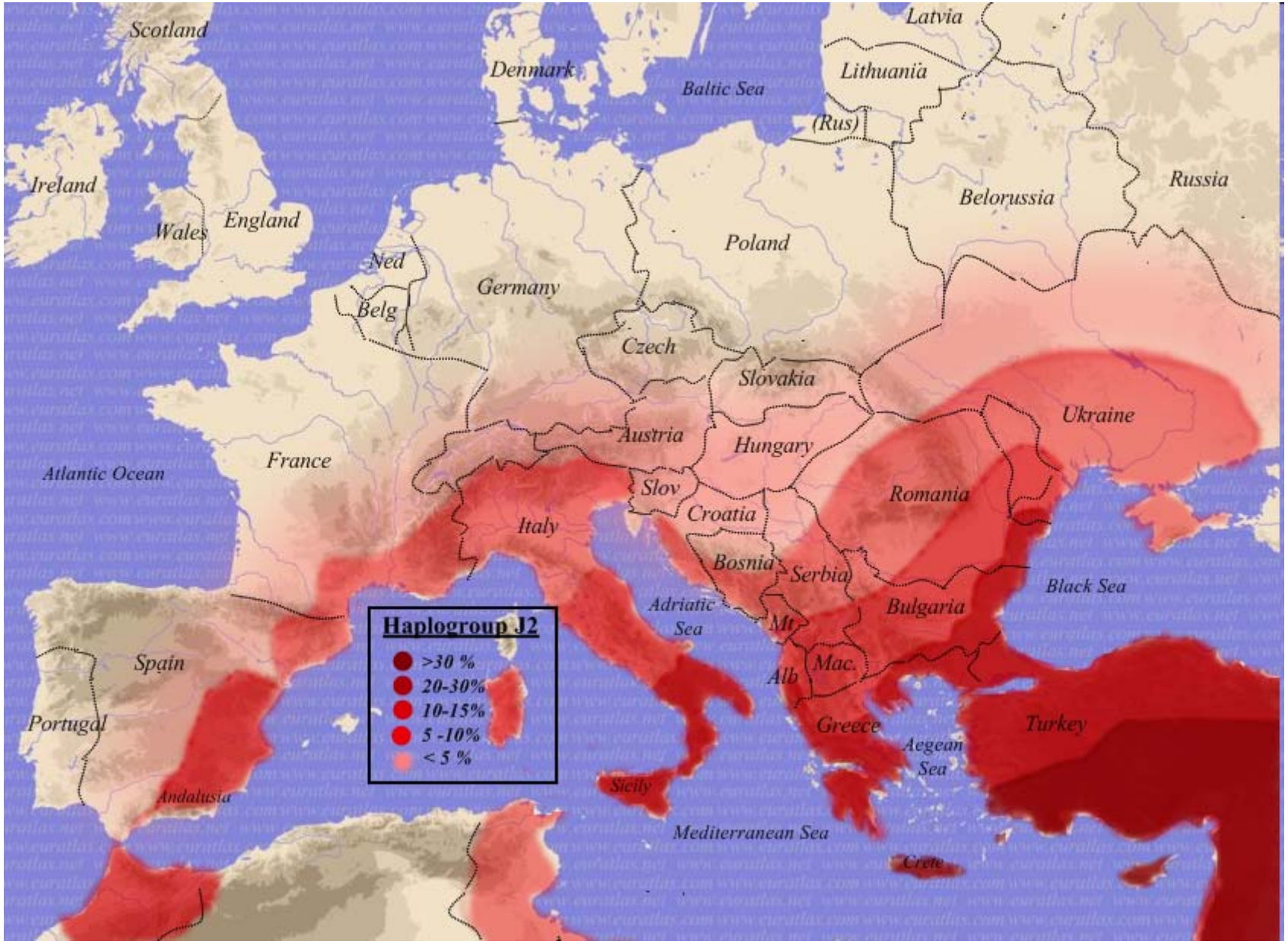
(But this is just one locus and not population history)



http://en.wikipedia.org/wiki/File:Map-of-human-migrations.jpg

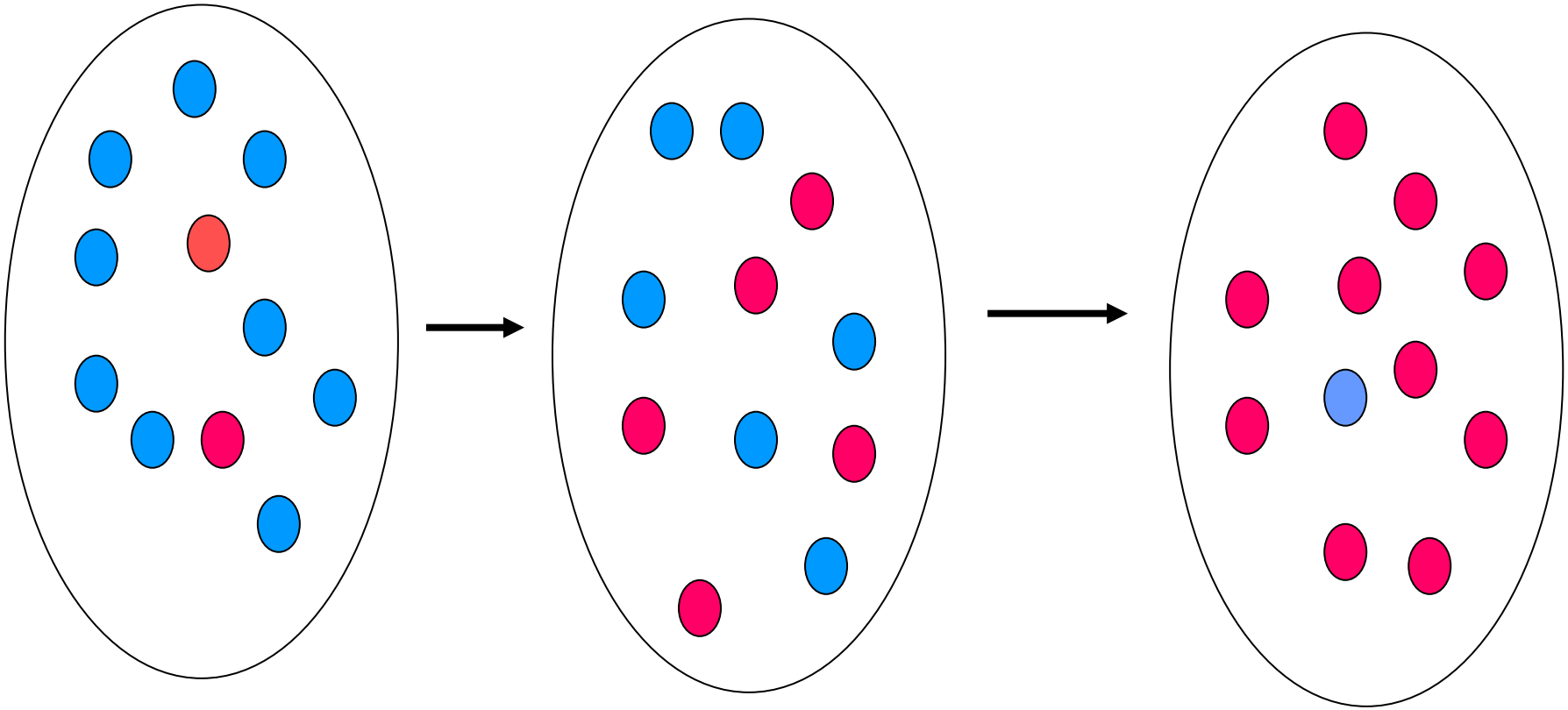
There are many other inherited traits, example B allele of ABO blood group



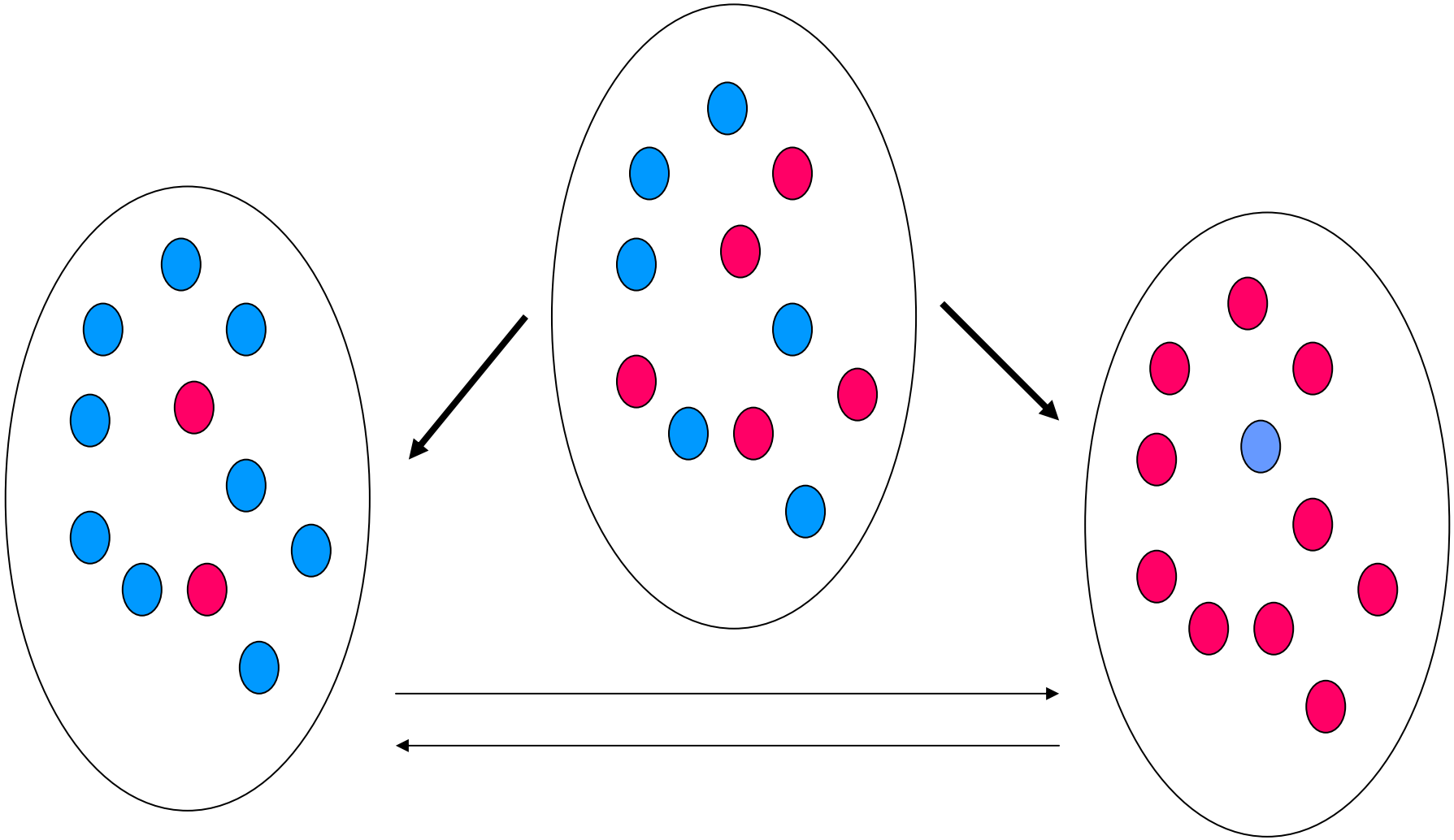


http://en.wikipedia.org/wiki/File:HaploJ2.png

Within populations, allele frequencies can “drift” over time

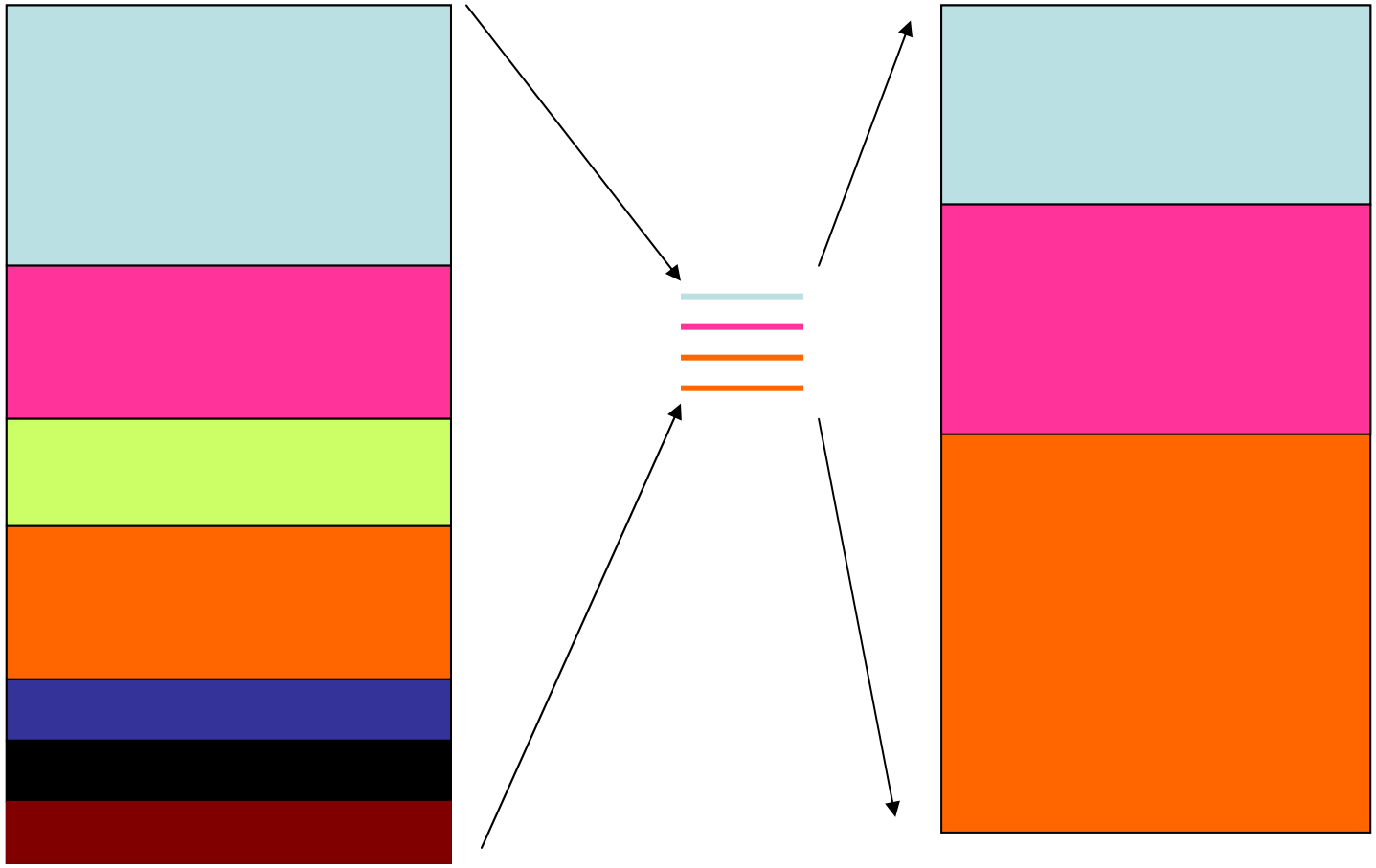


Genetic drift between populations

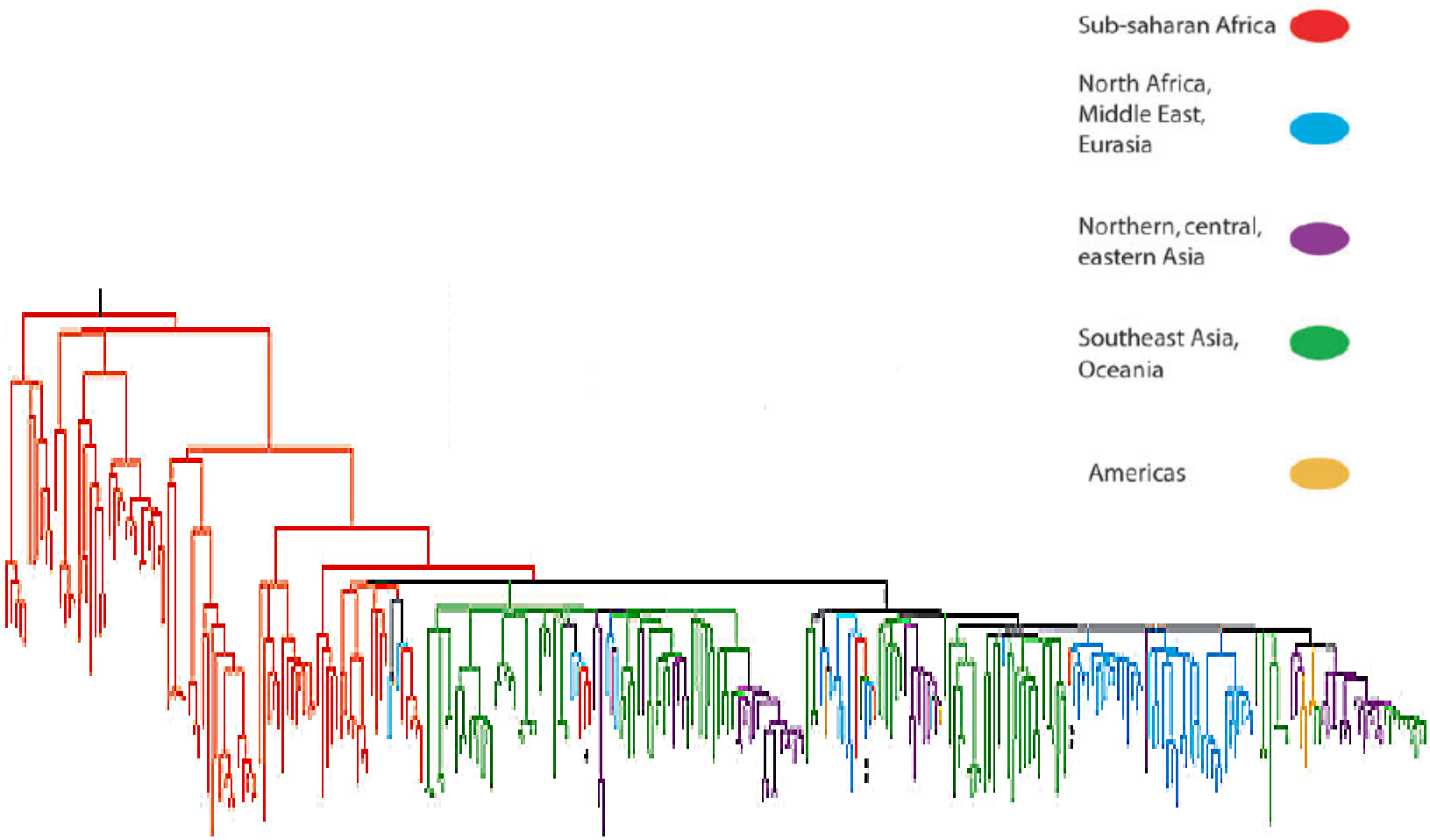


Random chance changes allele frequencies over time.
We can infer relationships between human populations.

Genetic Bottlenecks can result in less genetic variation

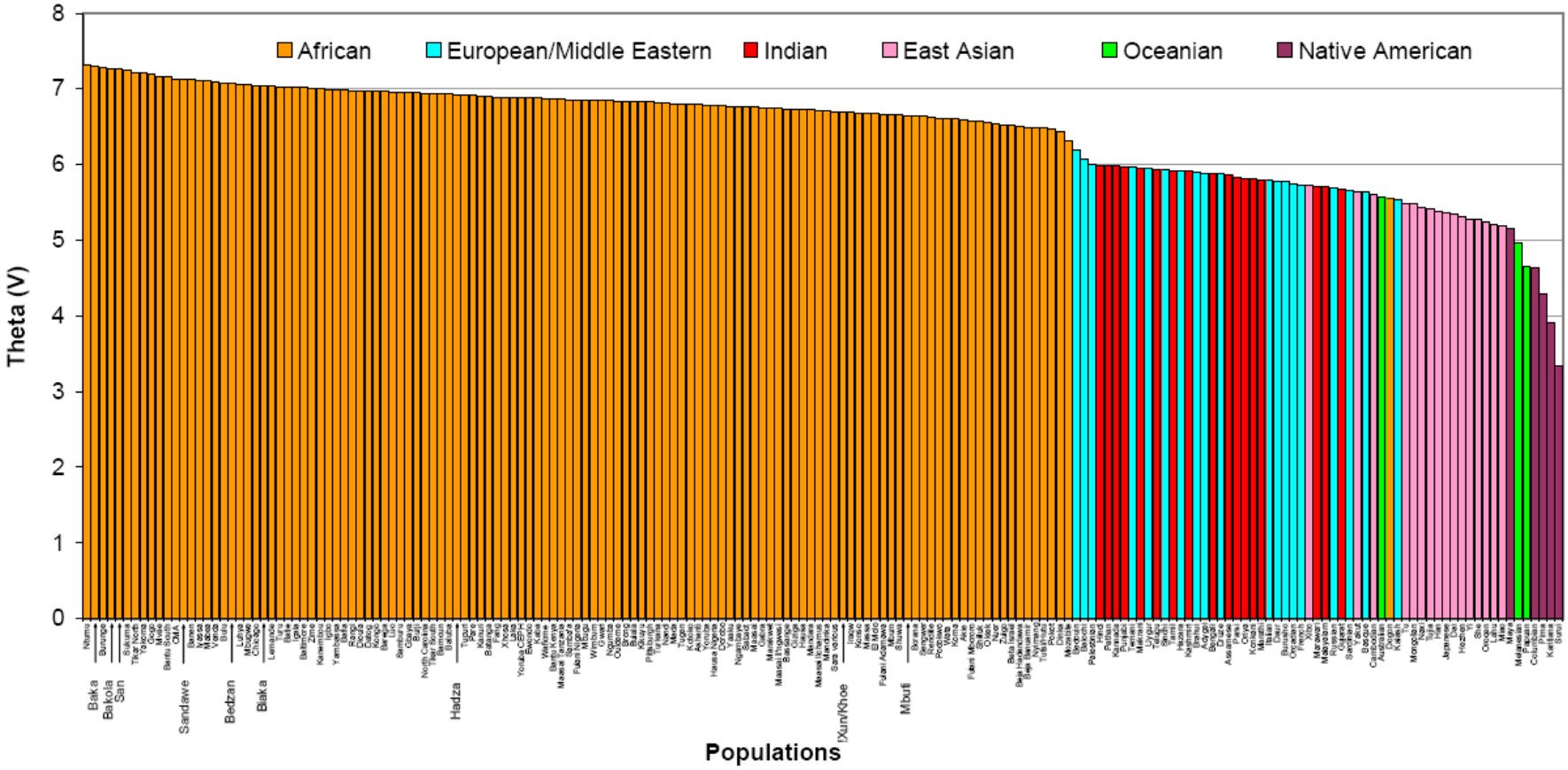


Less genetic variation outside of Africa

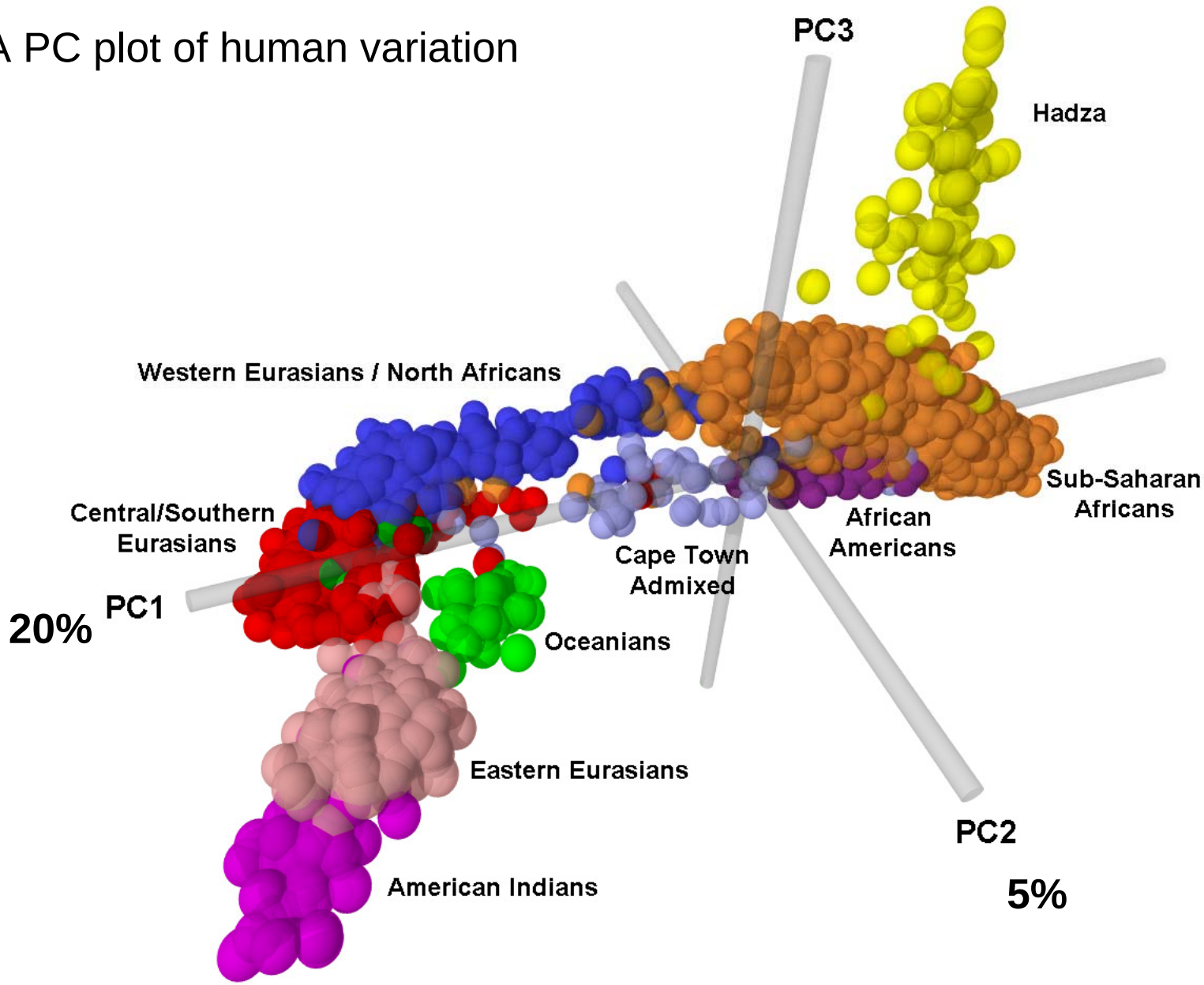


Gonder 2007 MBE 24:757

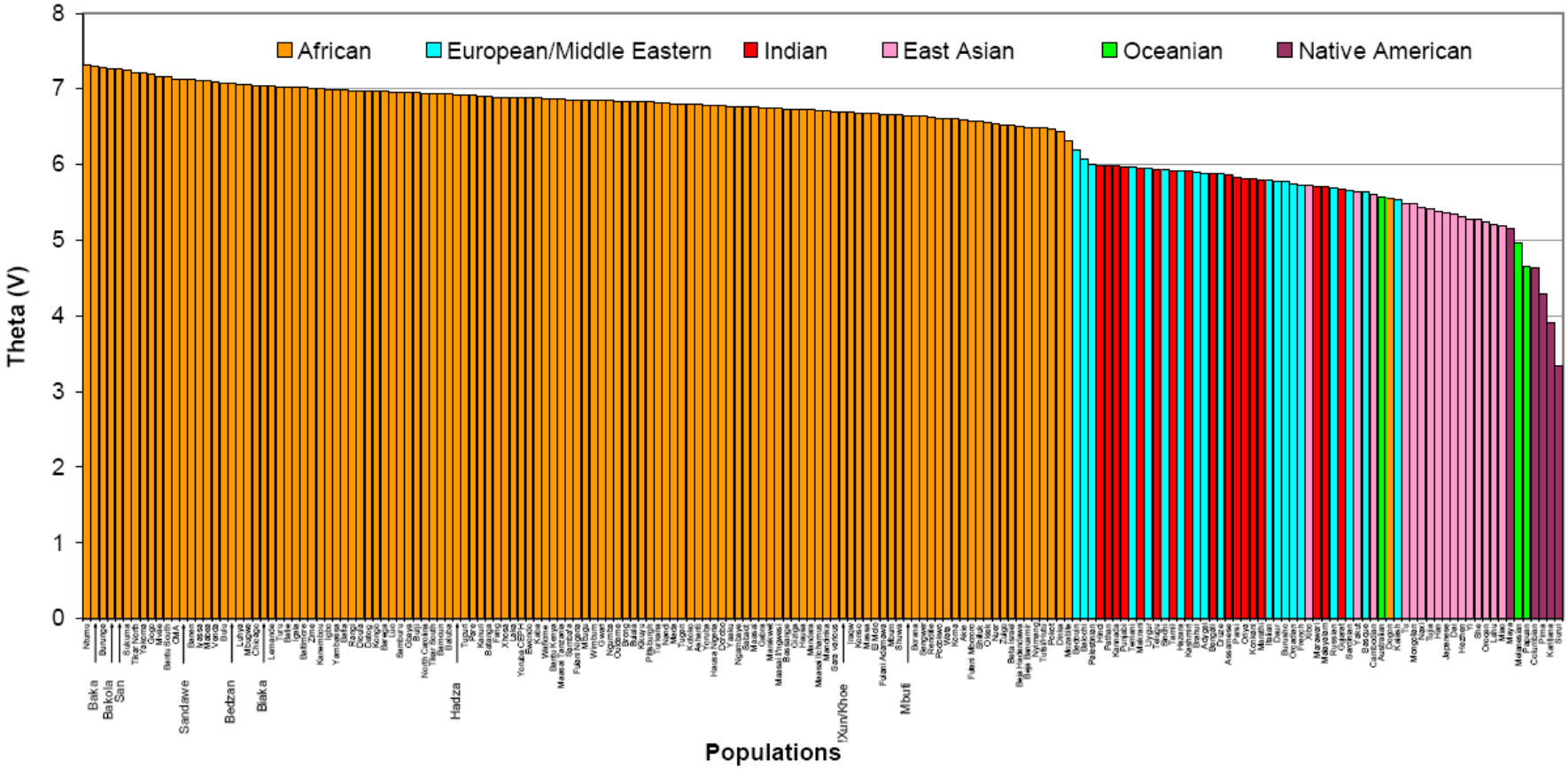
A general trend is a reduction in population genetic diversity away from an origin in Africa (from over 800 sites in the genome typed over 4,000 DNA samples)

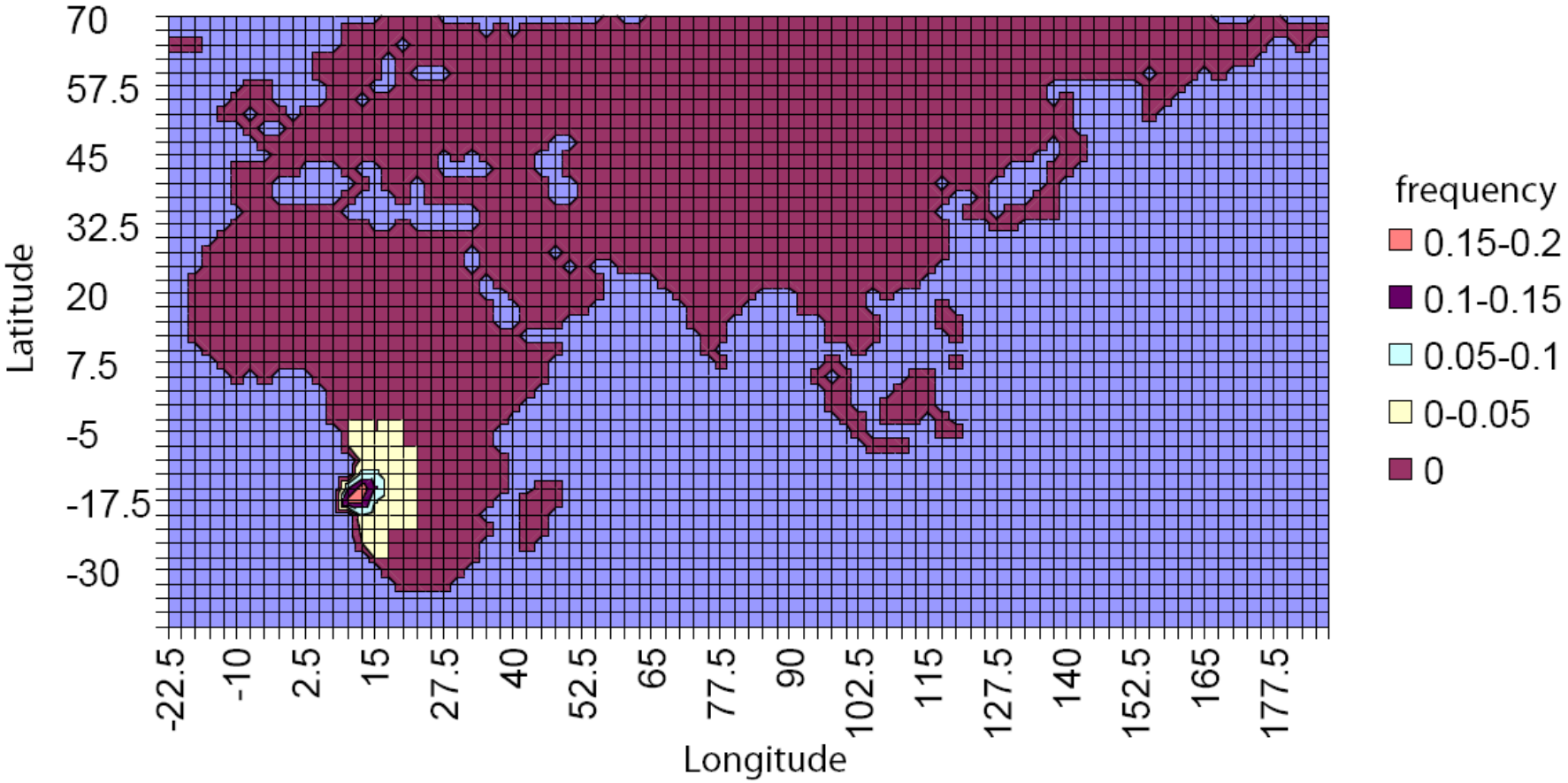


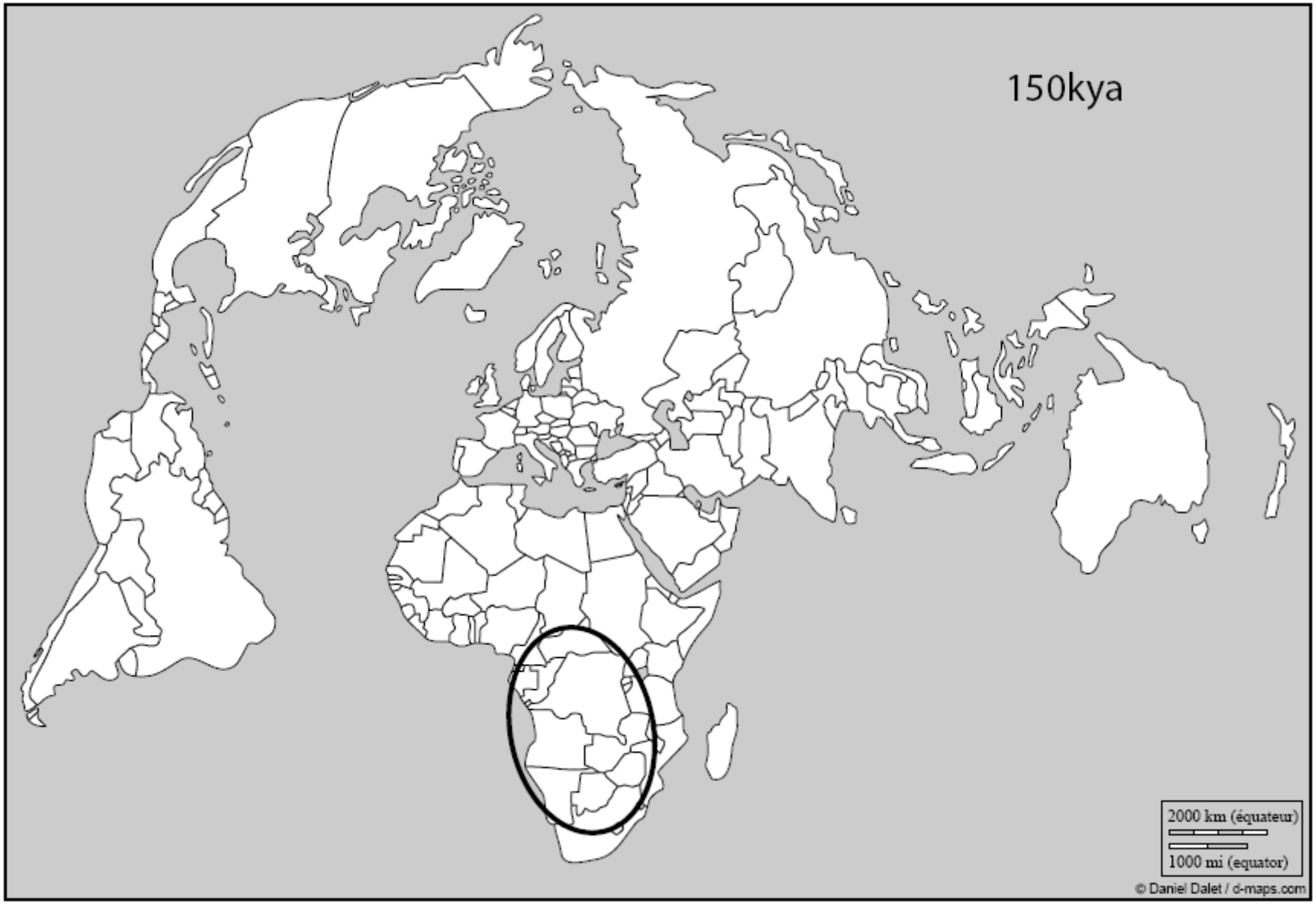
A PC plot of human variation

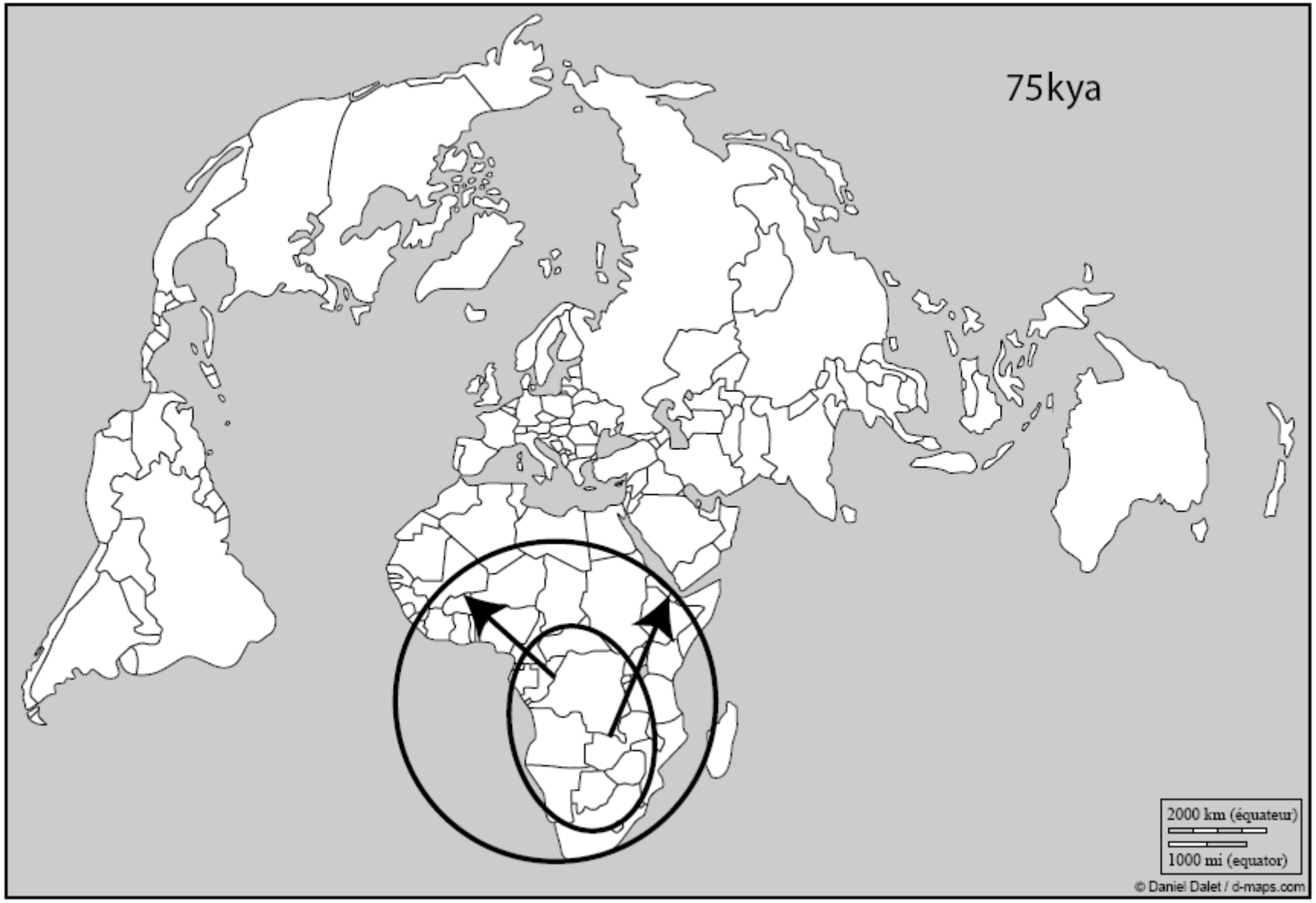


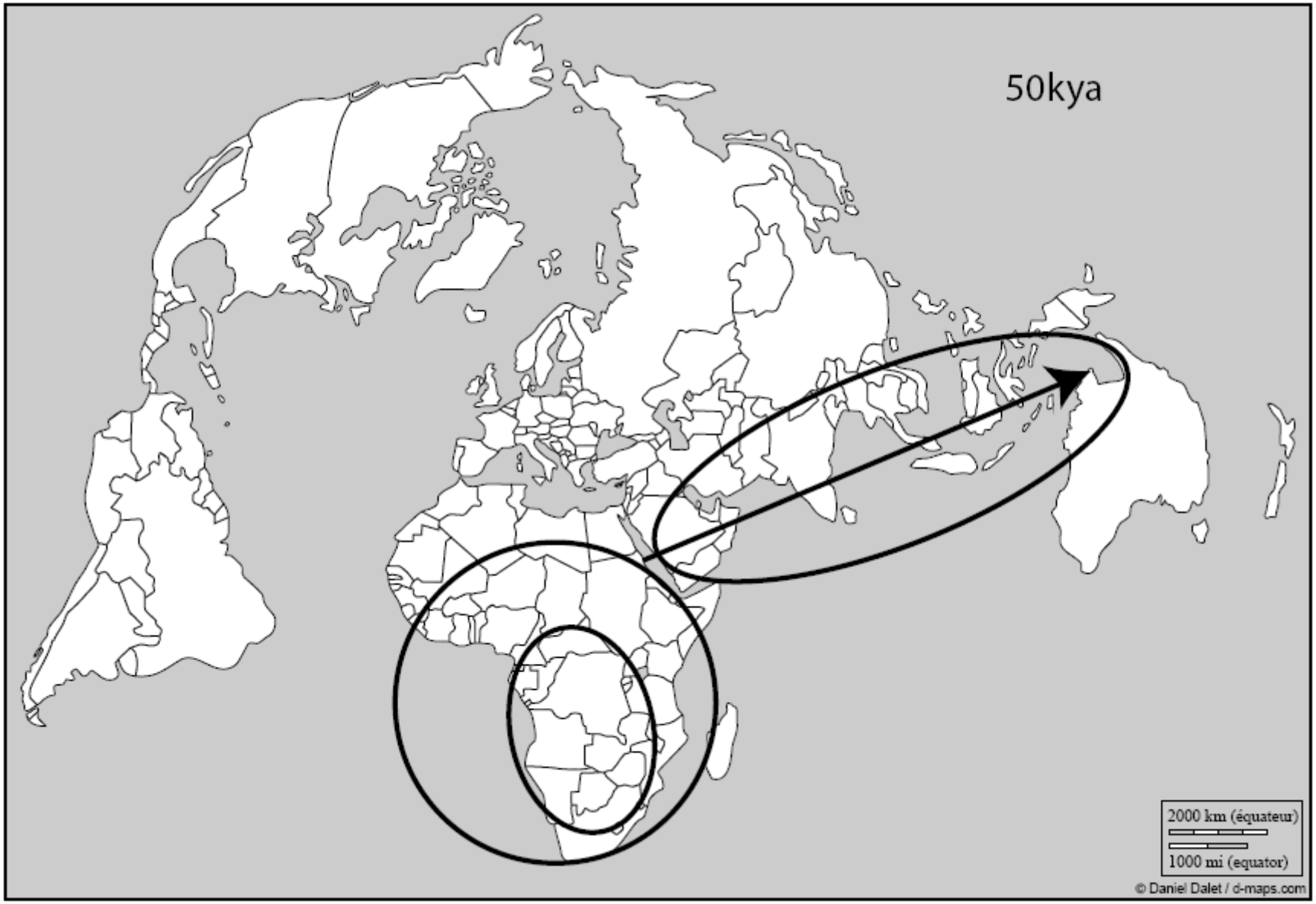
Can we follow the reduction in diversity backwards to find an origin of modern humans within Africa?

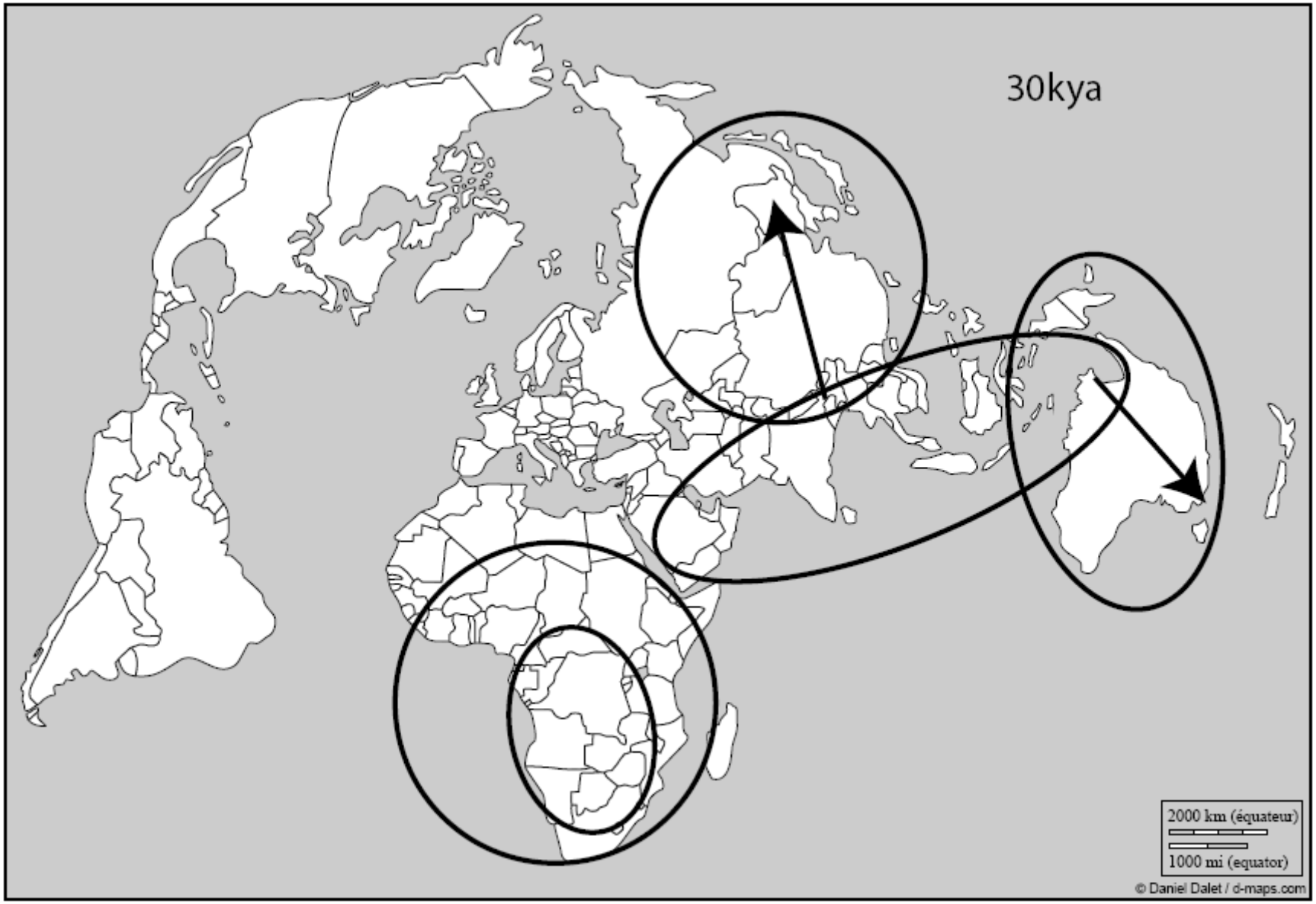


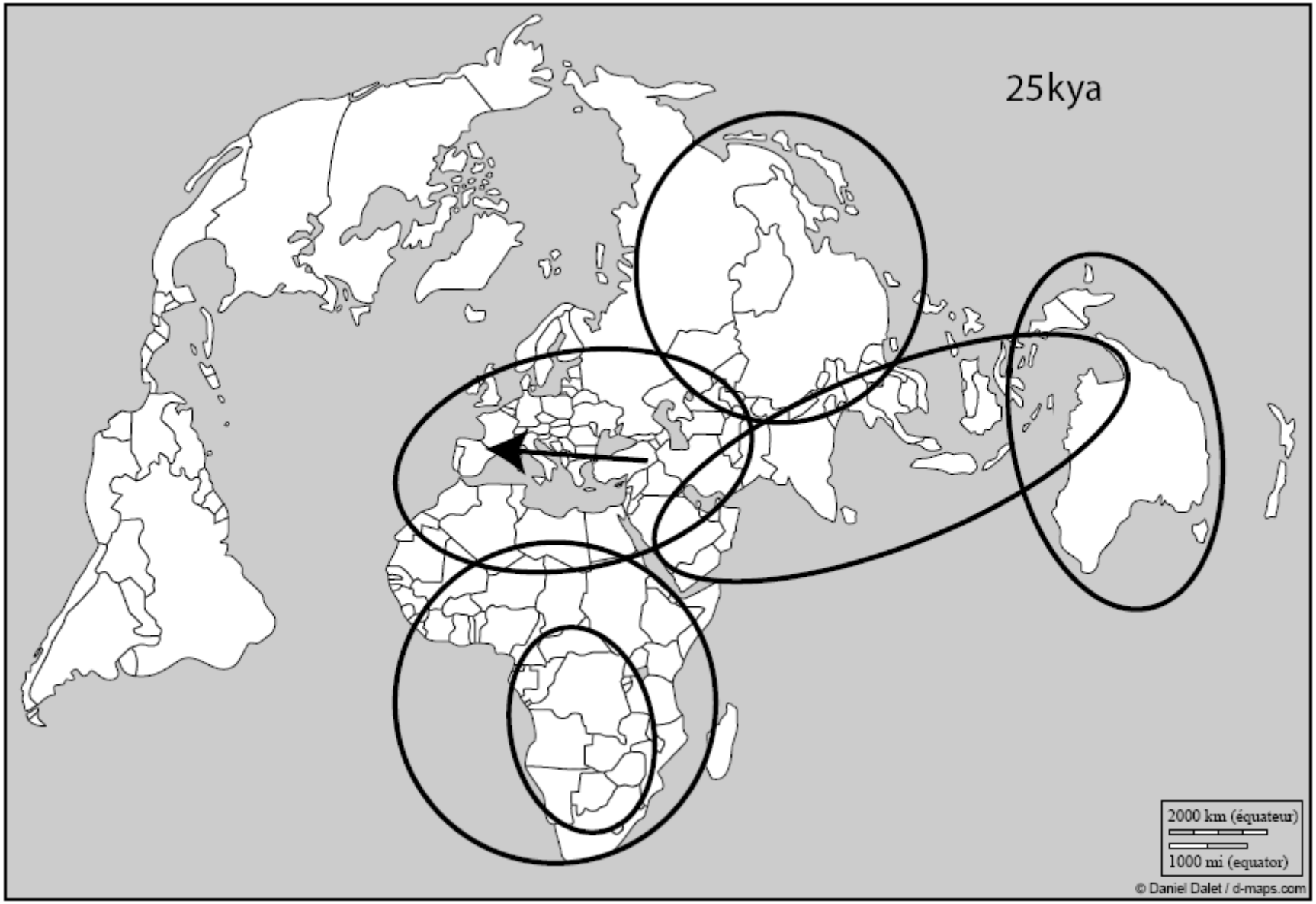

70
57.5
45
32.5
20
7.5
-5
-17.5
-30
Latitude
-22.5
-10
2.5
15
27.5
40
52.5
65
77.5
90
102.5
115
127.5
140
152.5
165
177.5
Longitude
frequency
0.15-0.2
0.1-0.15
0.05-0.1
0-0.05
0

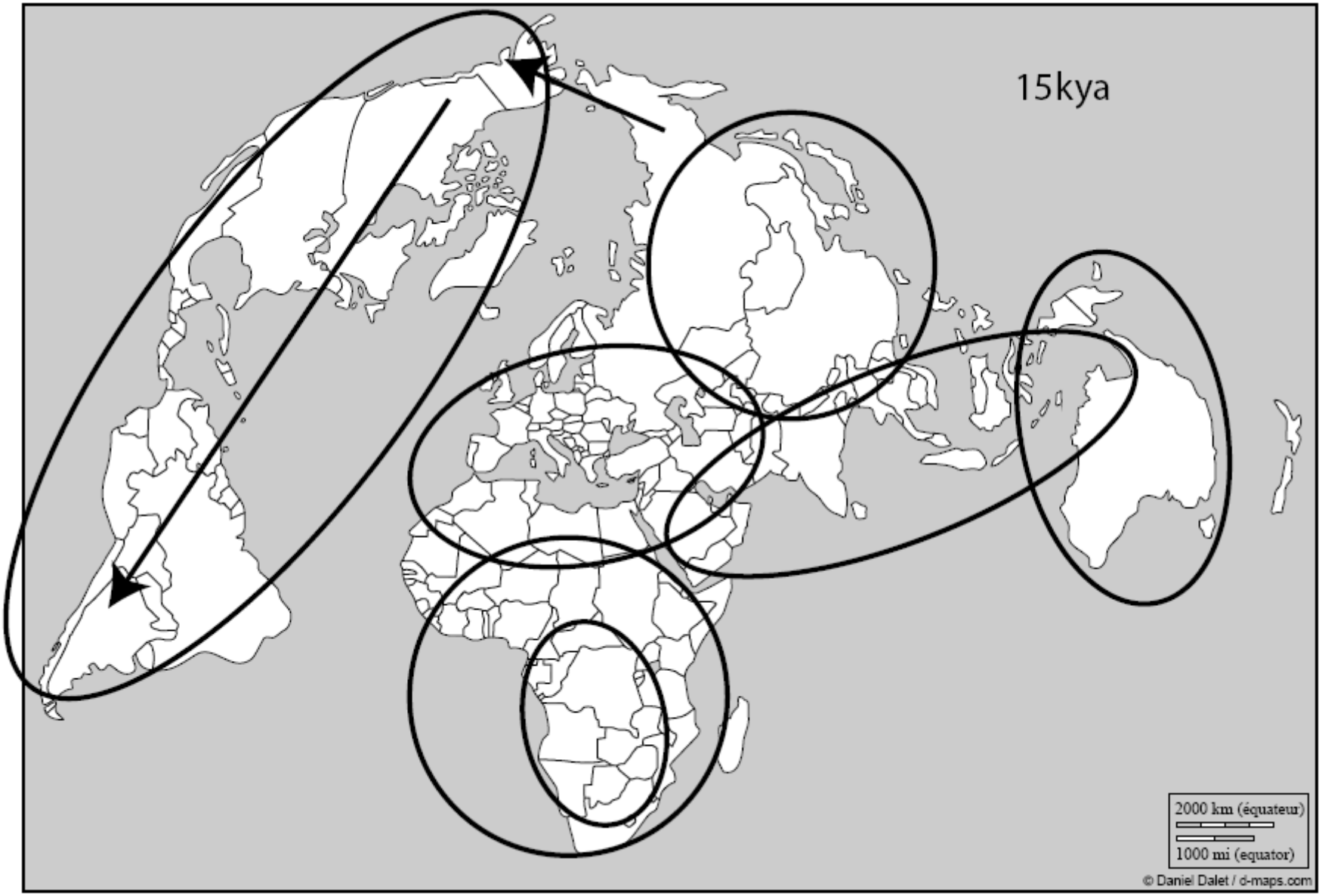

150kya
2000 km (équateur)
1000 mi (equator)
© Daniel Dalet / d-maps.com


75kya
2000 km (équateur)
1000 mi (equator)
© Daniel Dalet / d-maps.com

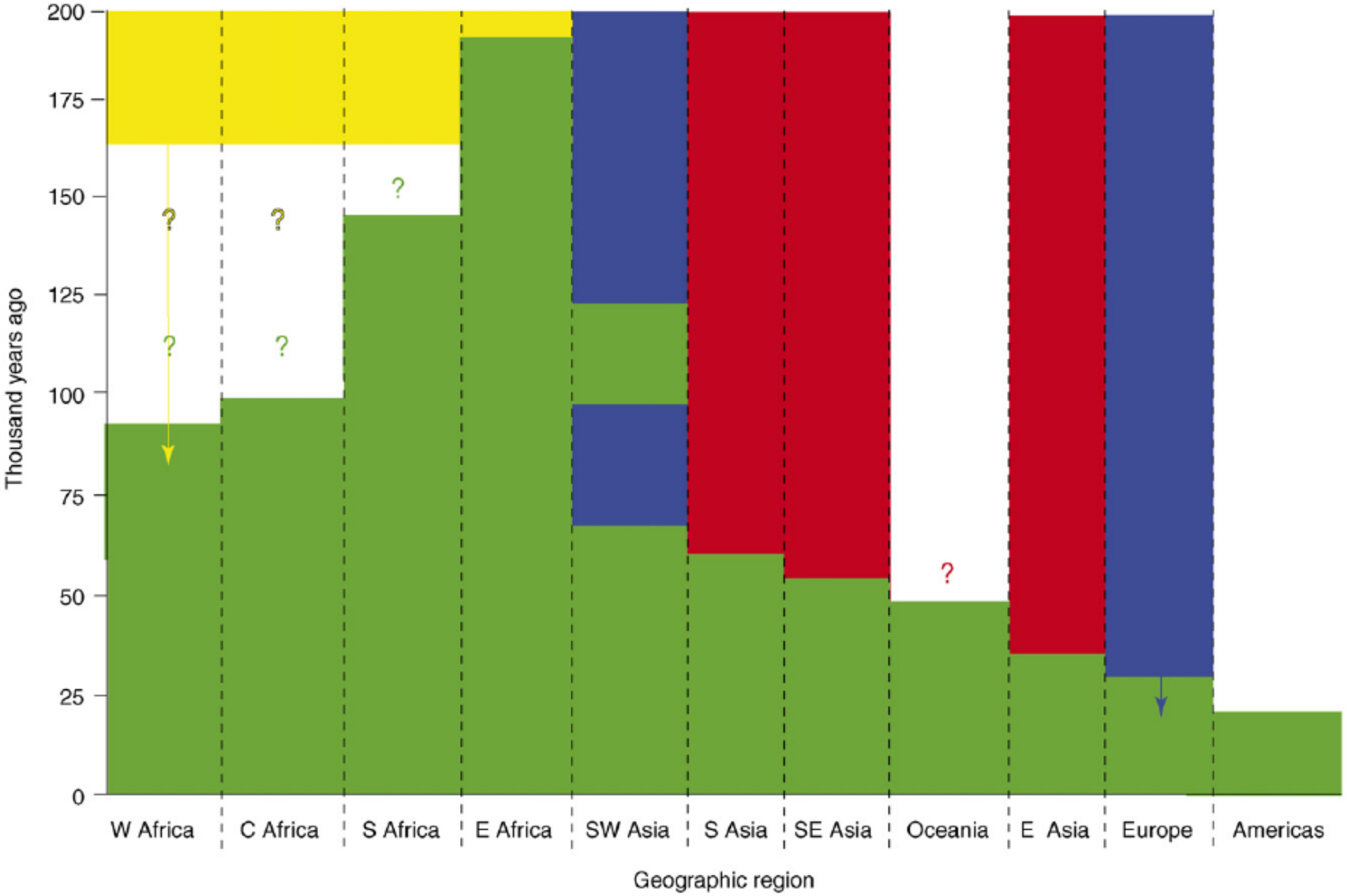

50kya
2000 km (équateur)
1000 mi (equator)
© Daniel Dalet / d-maps.com


30kya
2000 km (équateur)
1000 mi (equator)
© Daniel Dalet / d-maps.com

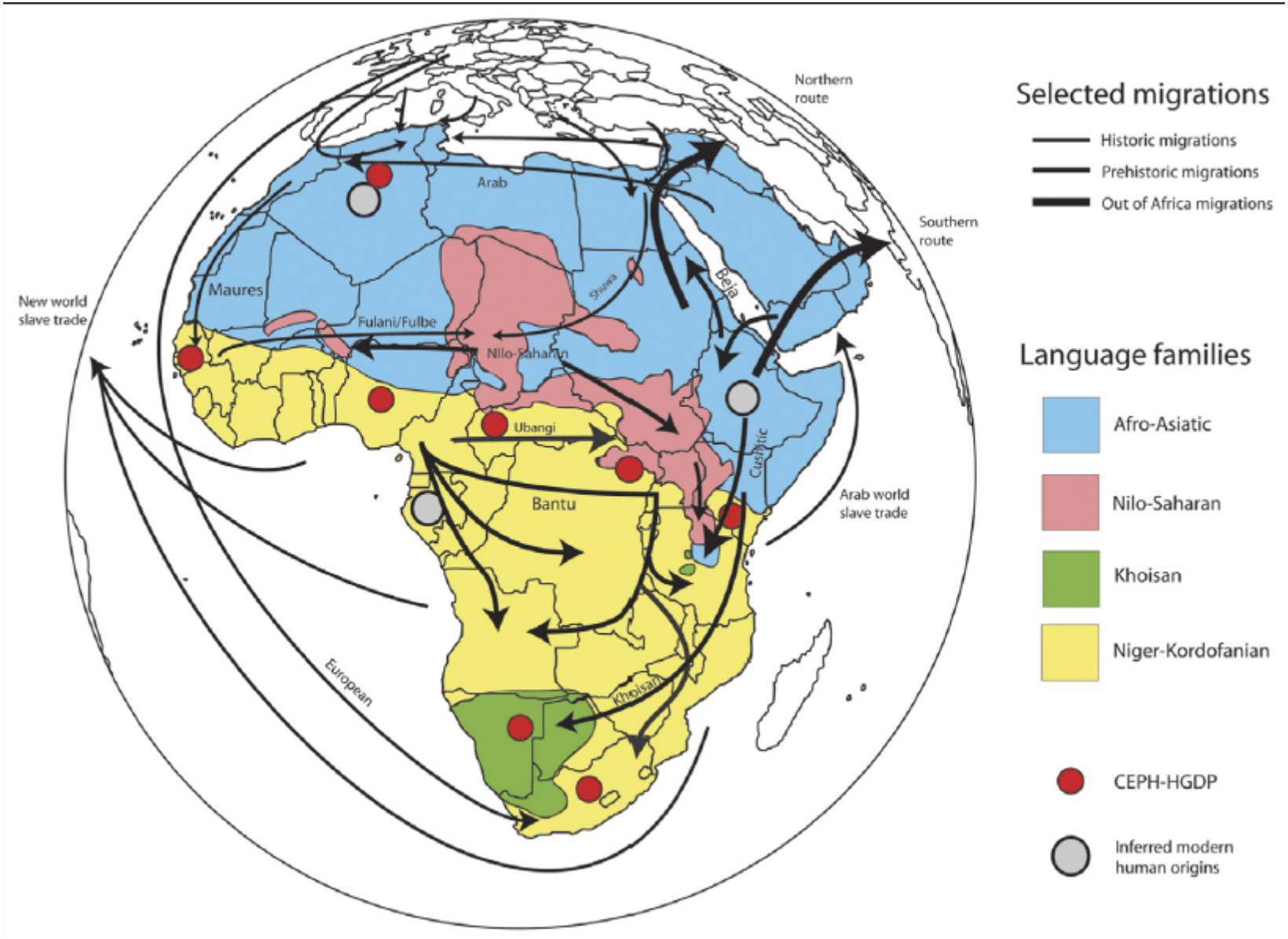

25kya
2000 km (équateur)
1000 mi (equator)
© Daniel Dalet / d-maps.com


15kya
2000 km (équateur)
1000 mi (equator)
© Daniel Dalet / d-maps.com

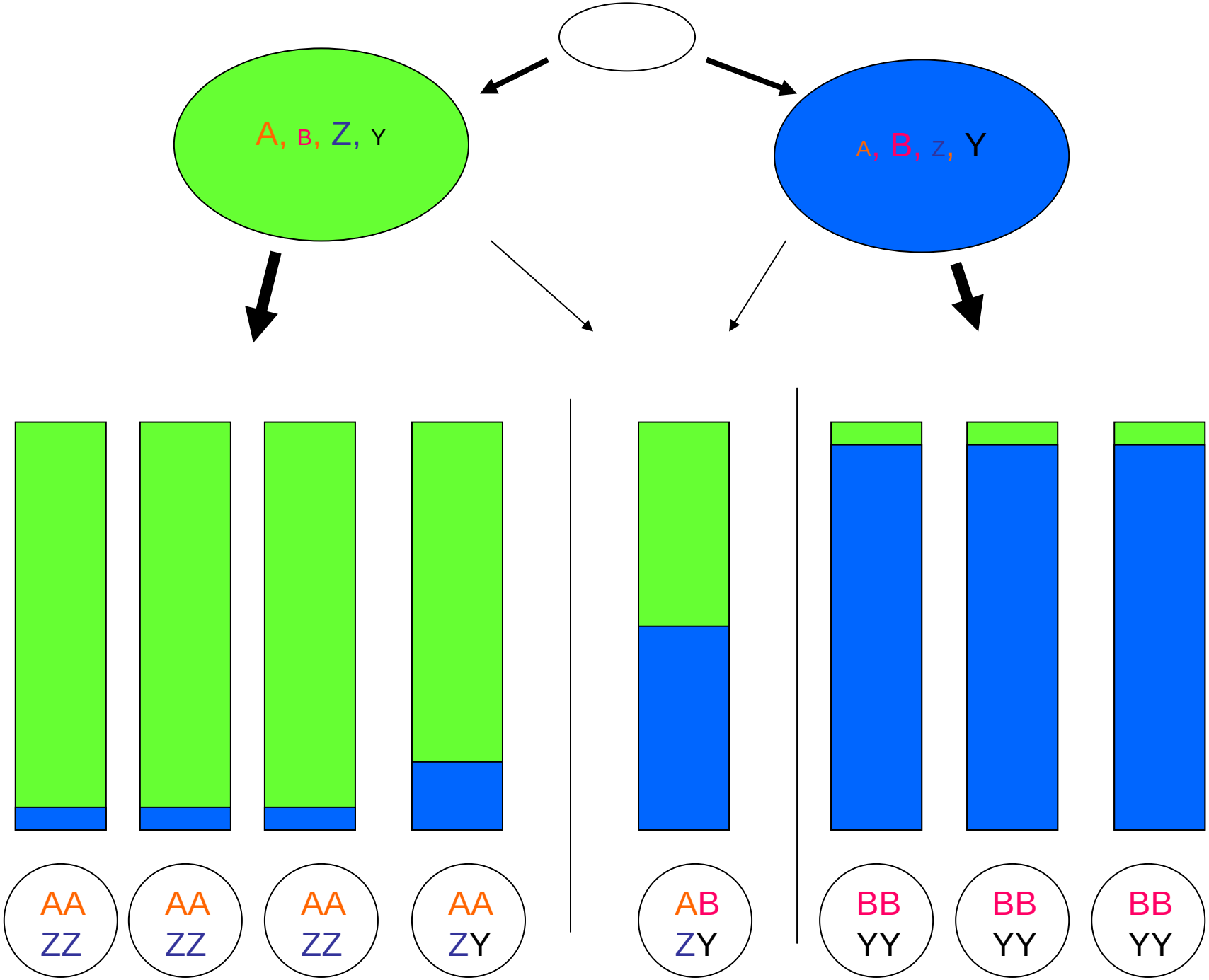
An emerging picture of modern human geographic expansion

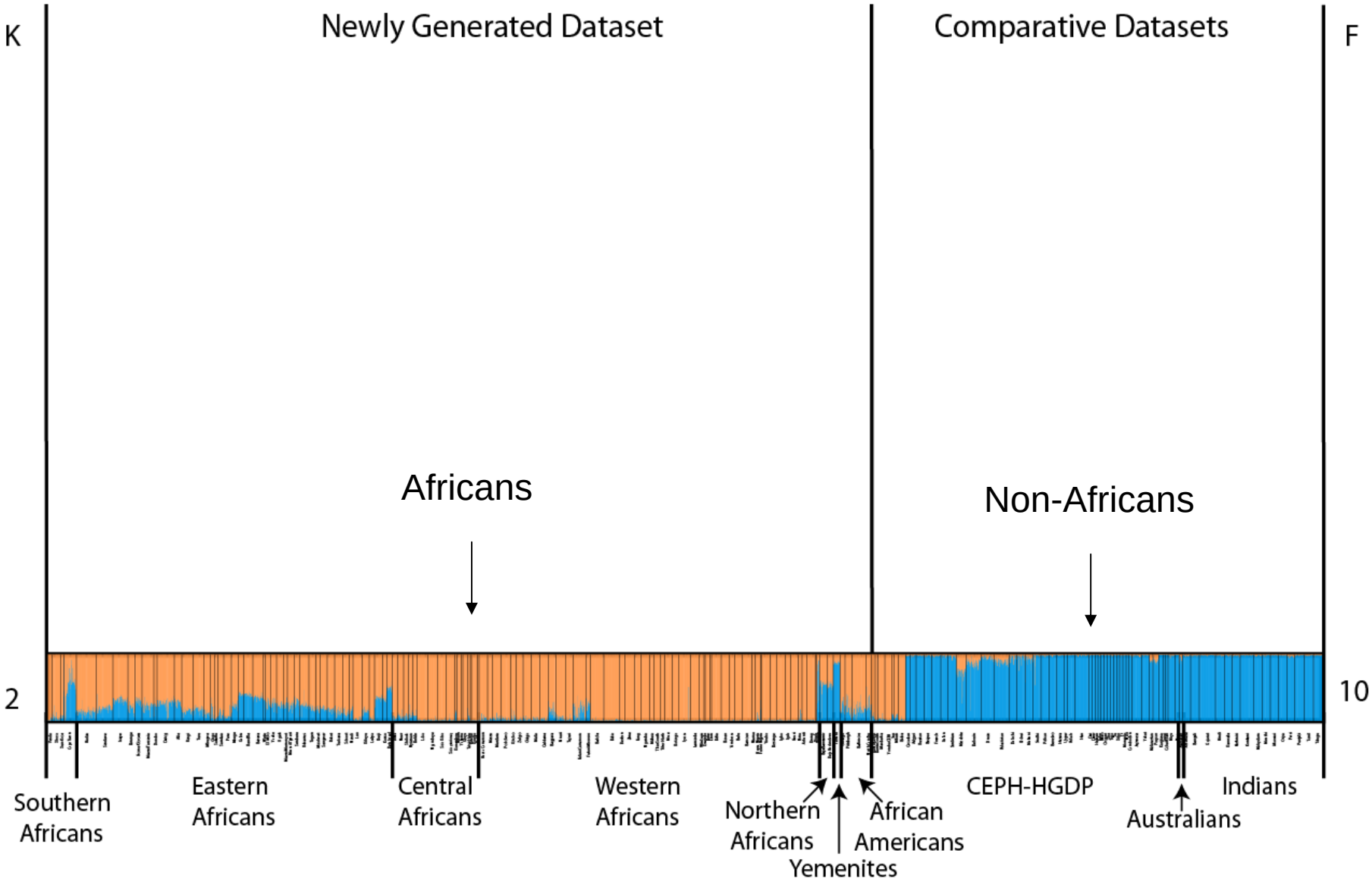


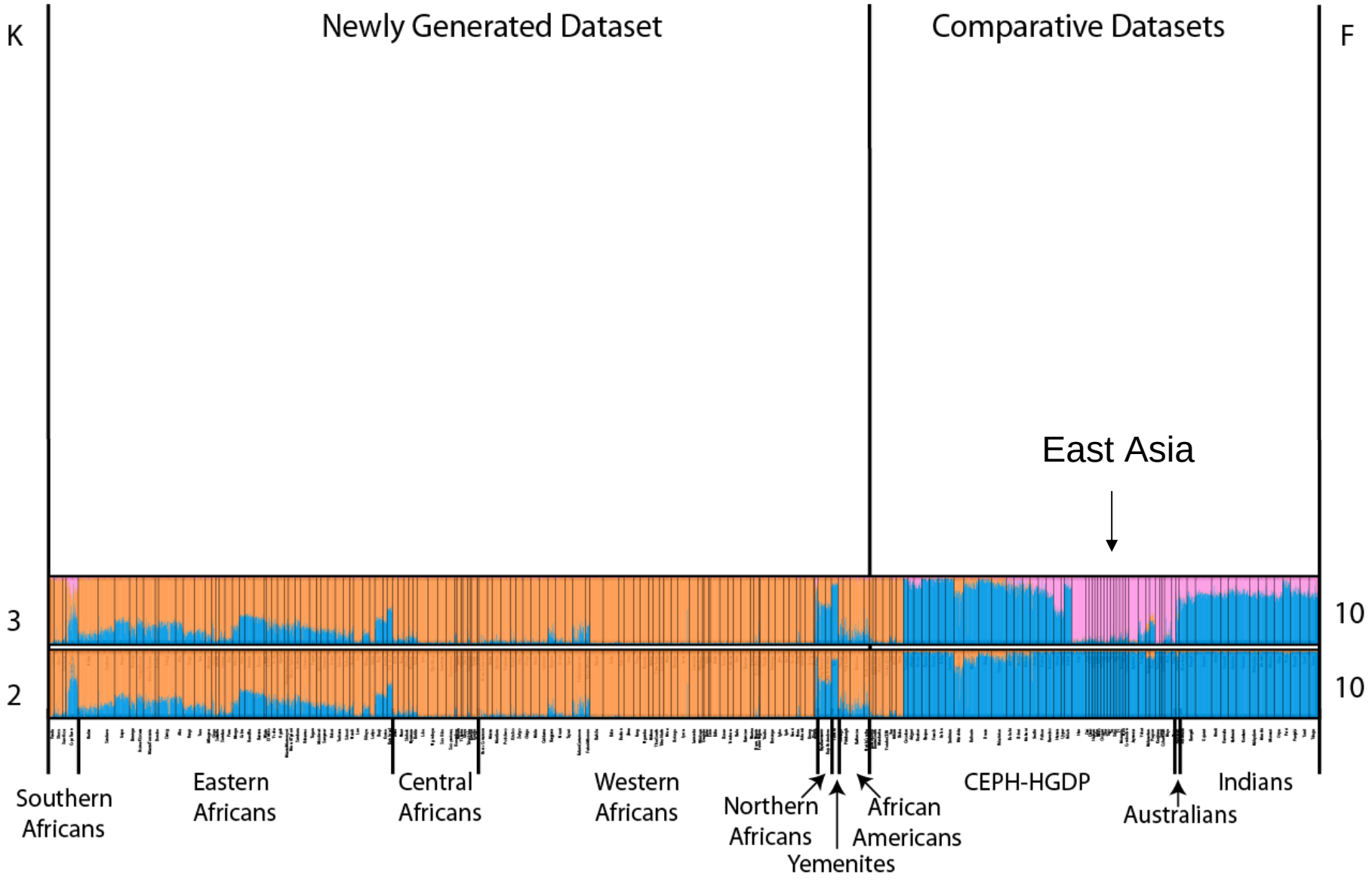
Reed & Tishkoff 2006

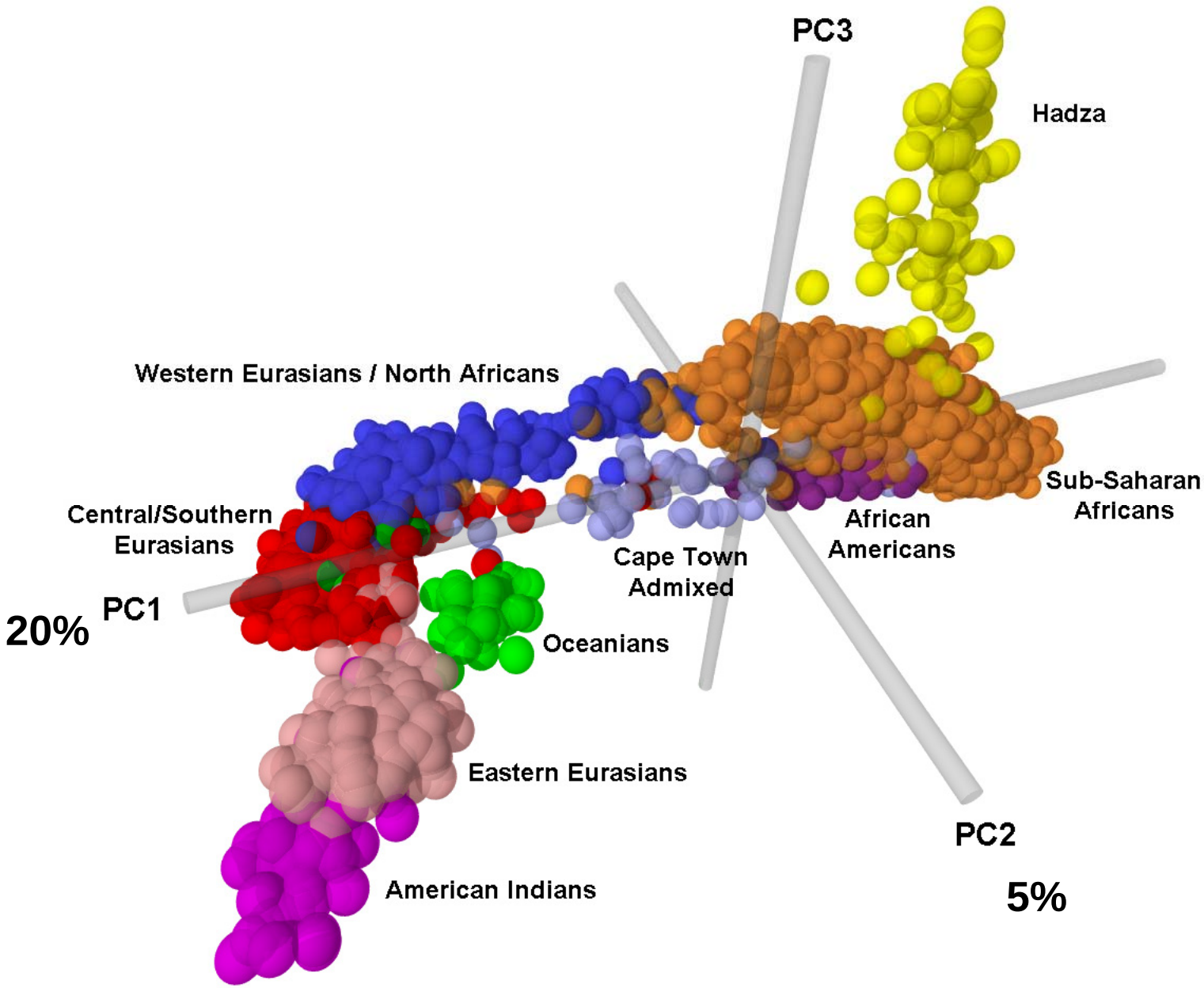


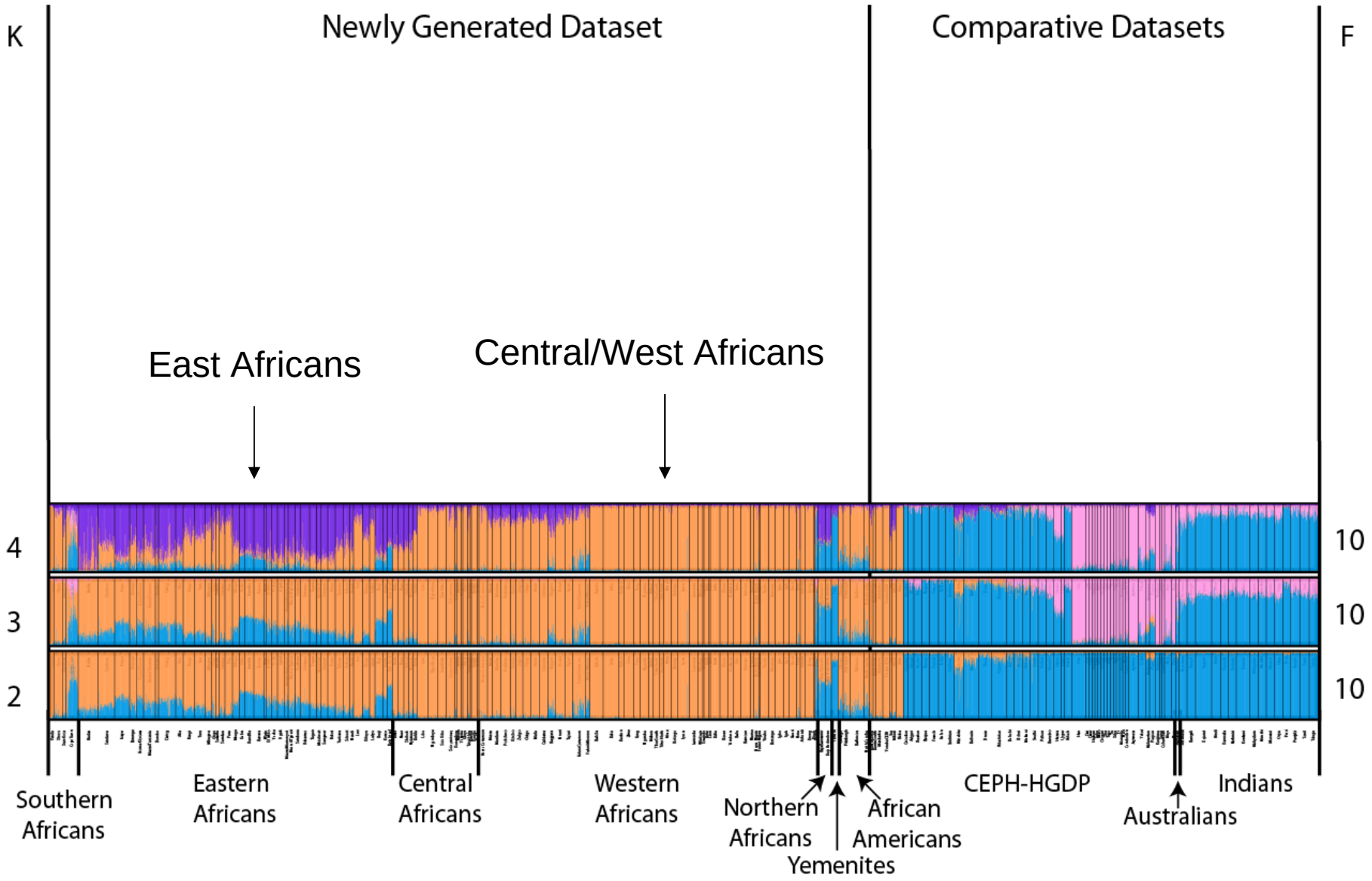
Reed & Tishkoff 2006

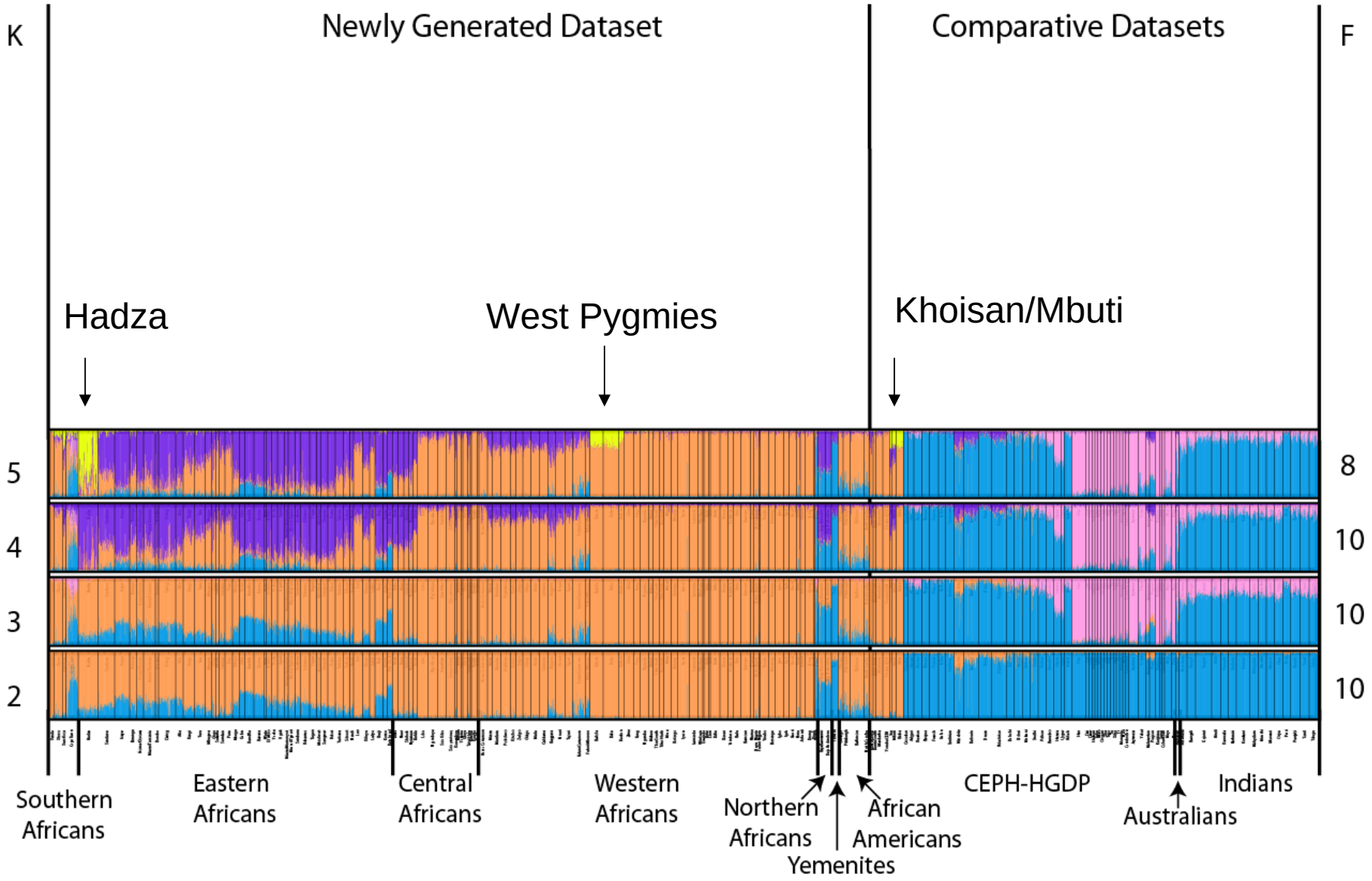

A, B, Z, Y
A, B, Z, Y
AA
ZZ
AA
ZZ
AA
ZZ
AA
ZY
AB
ZY
BB
YY
BB
YY
BB
YY

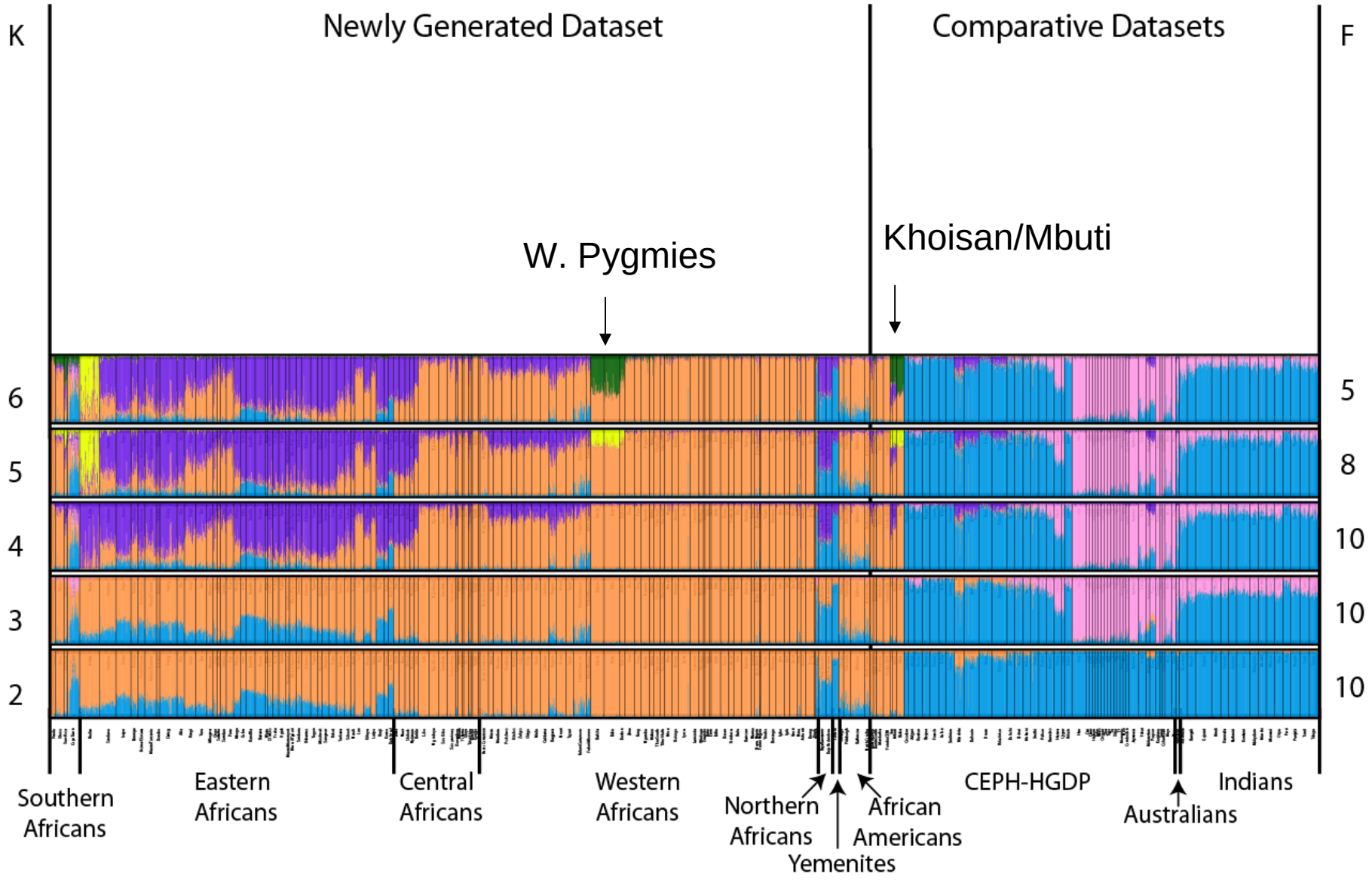

K
Newly Generated Dataset
Comparative Datasets
F
Africans
Non-Africans
2
10
Southern Africans
Eastern Africans
Central Africans
Western Africans
Northern Africans
Yemenites
African Americans
CEPH-HGDP
Australians
Indians

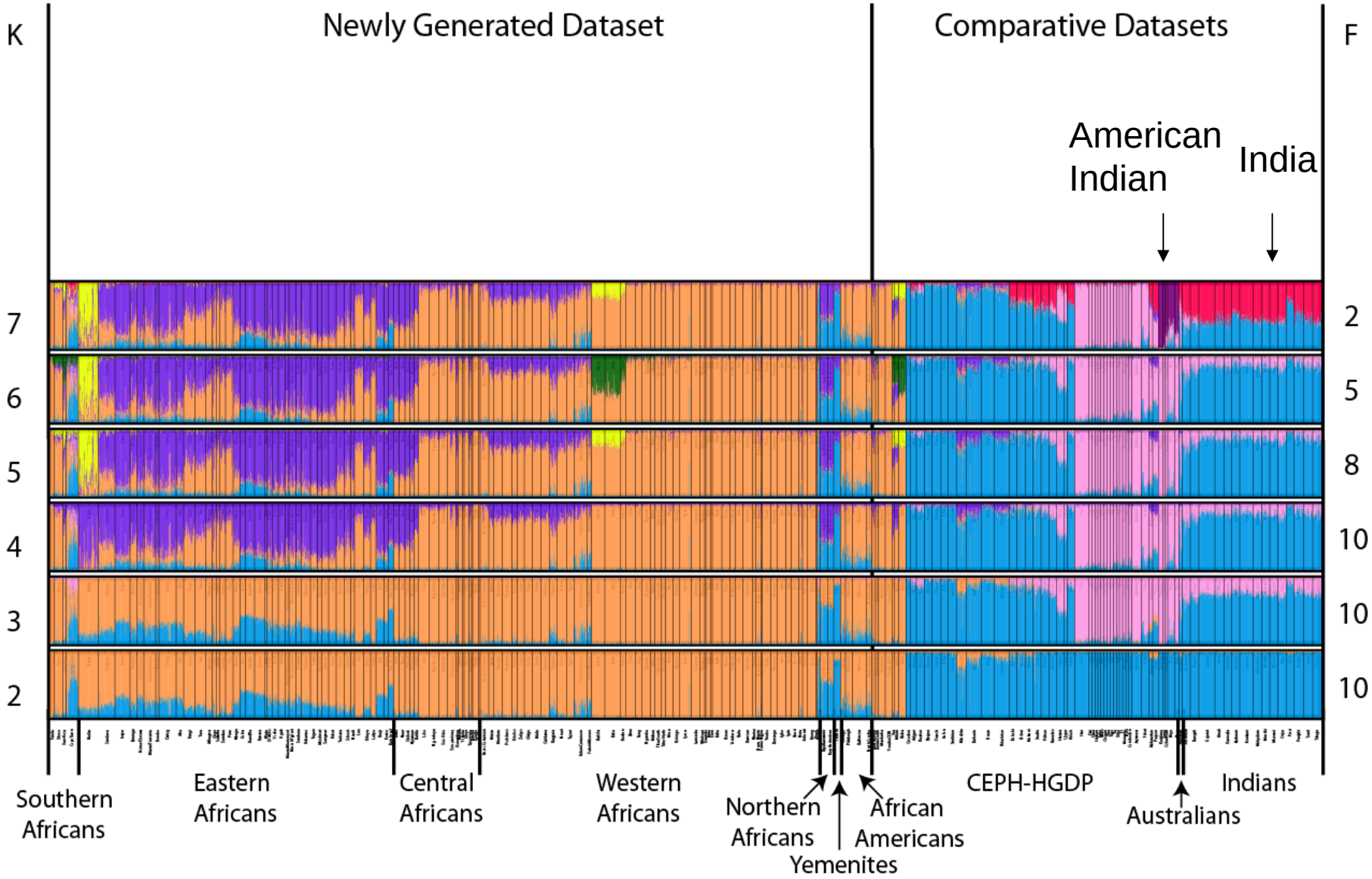

K
Newly Generated Dataset
Comparative Datasets
F
East Asia
3
2
10
10
Southern Africans
Eastern Africans
Central Africans
Western Africans
Northern Africans
Yemenites
African Americans
CEPH-HGDP
Australians
Indians

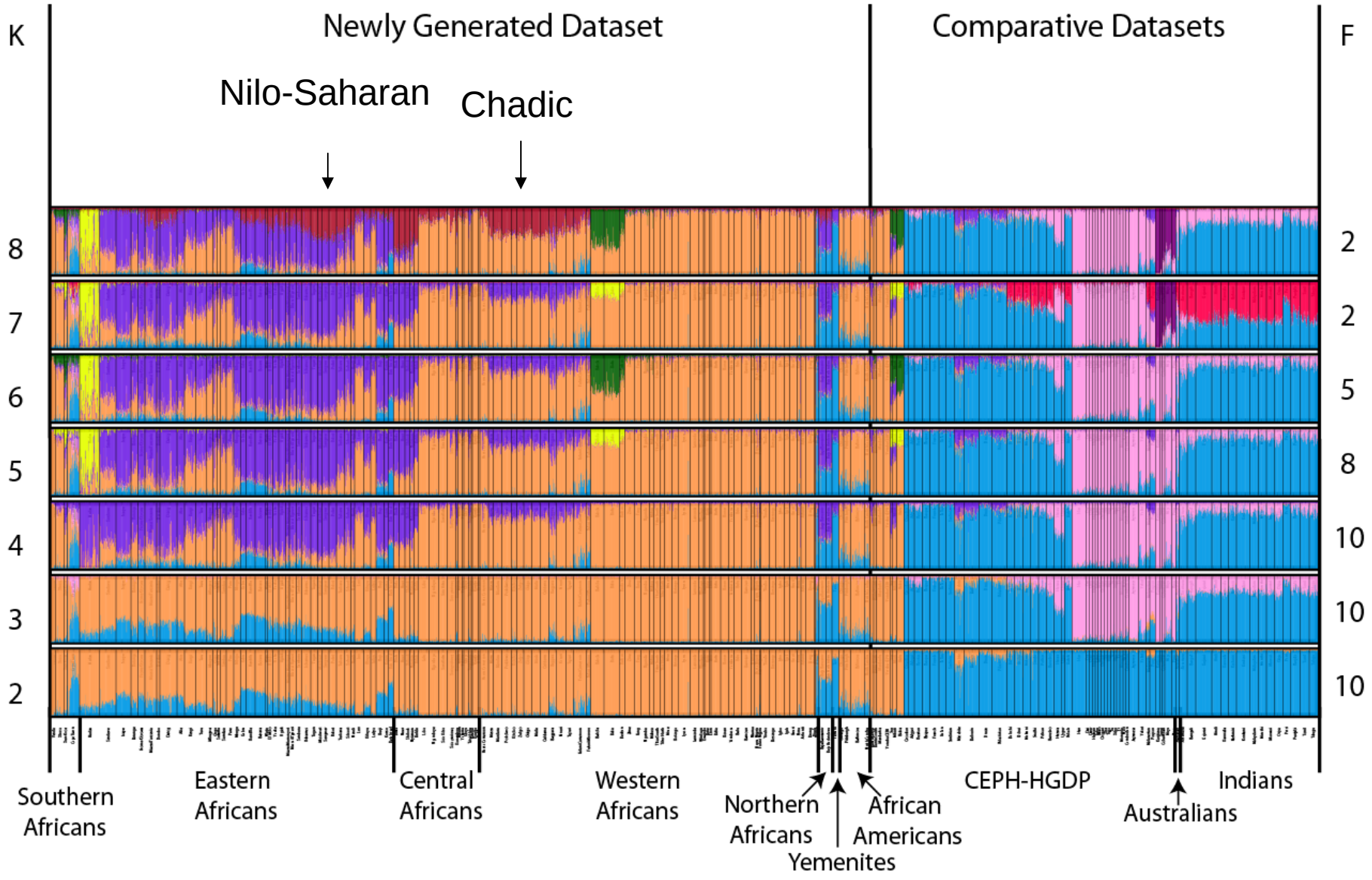

PC3
Hadza
Western Eurasians / North Africans
Sub-Saharan
Africans
Central/Southern
Eurasians
African
Americans
Cape Town
Admixed
20%
PC1
Oceanians
Eastern Eurasians
PC2
American Indians
5%

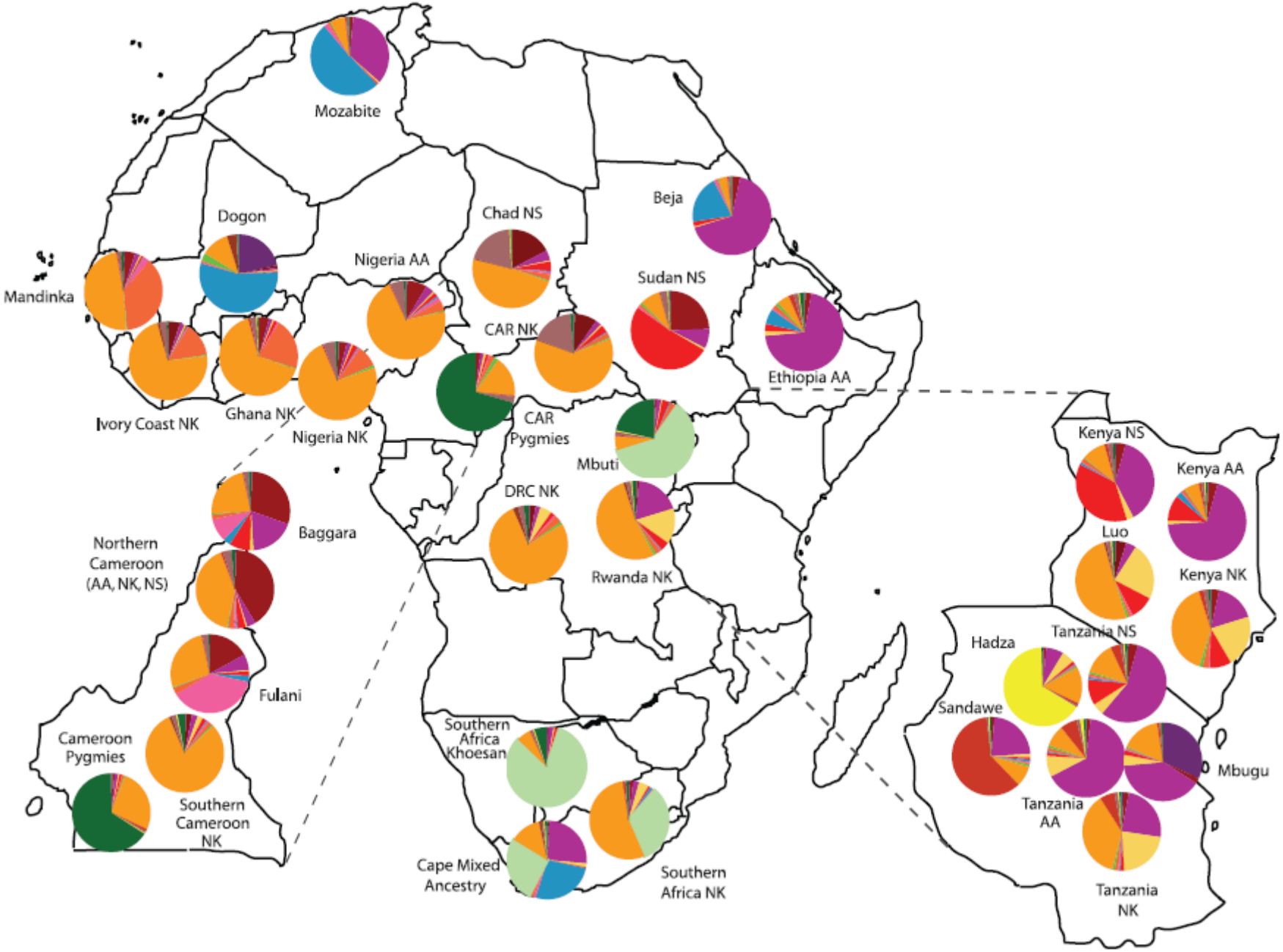

K
Newly Generated Dataset
Comparative Datasets
F
East Africans
Central/West Africans
4
3
2
10
10
10
Southern Africans
Eastern Africans
Central Africans
Western Africans
Northern Africans
Yemenites
African Americans
CEPH-HGDP
Australians
Indians


K
Newly Generated Dataset
Comparative Datasets
F
Hadza
West Pygmies
Khoisan/Mbuti
5
4
3
2
8
10
10
10
Southern Africans
Eastern Africans
Central Africans
Western Africans
Northern Africans
Yemenites
African Americans
CEPH-HGDP
Australians
Indians

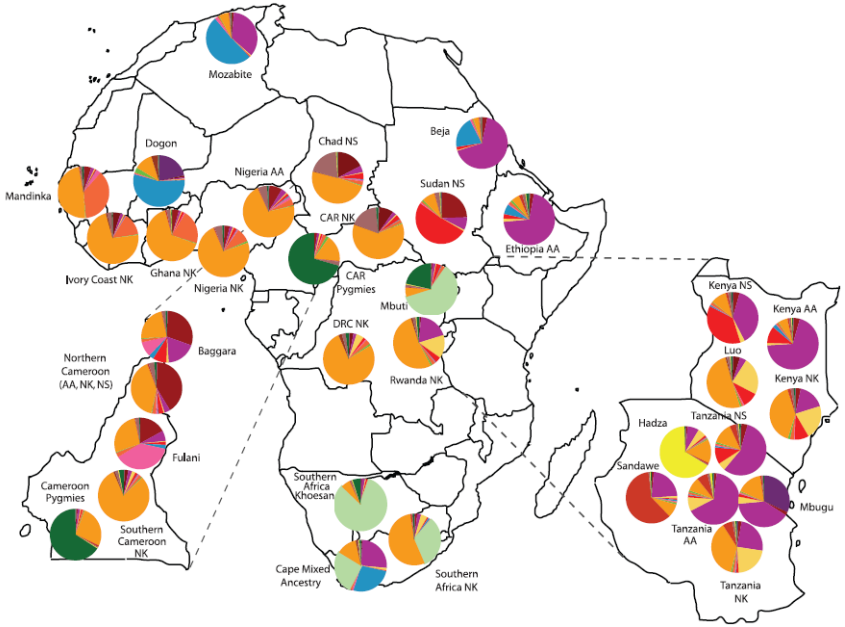

K
Newly Generated Dataset
Comparative Datasets
F
W. Pygmies
Khoisan/Mbuti
6
5
4
3
2
5
8
10
10
10
Southern Africans
Eastern Africans
Central Africans
Western Africans
Northern Africans
Yemenites
African Americans
CEPH-HGDP
Australians
Indians

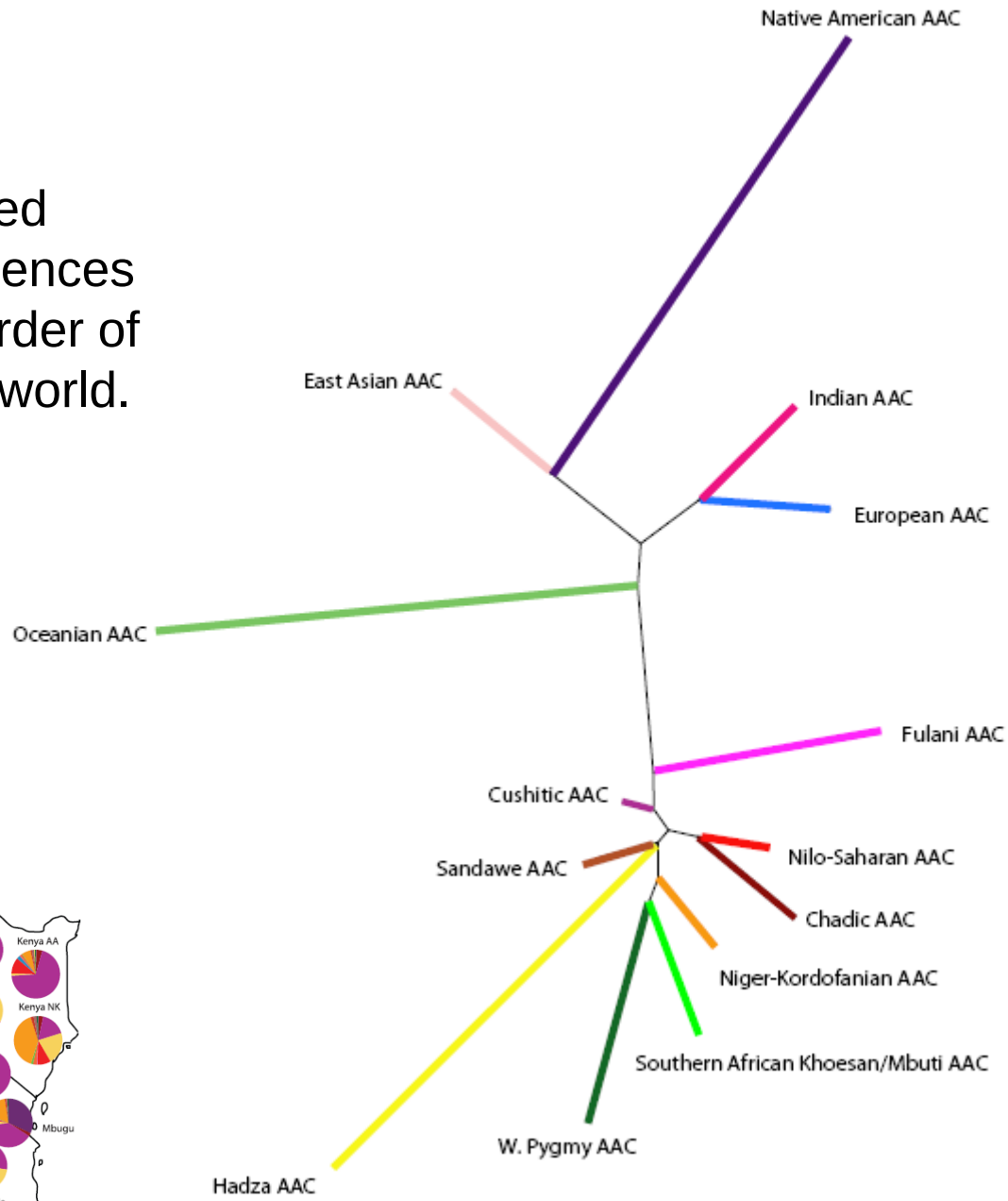

K
Newly Generated Dataset
Comparative Datasets
F
American Indian
India
7
6
5
4
3
2
2
5
8
10
10
10
Southern Africans
Eastern Africans
Central Africans
Western Africans
Northern Africans
Yemenites
African Americans
CEPH-HGDP
Australians
Indians

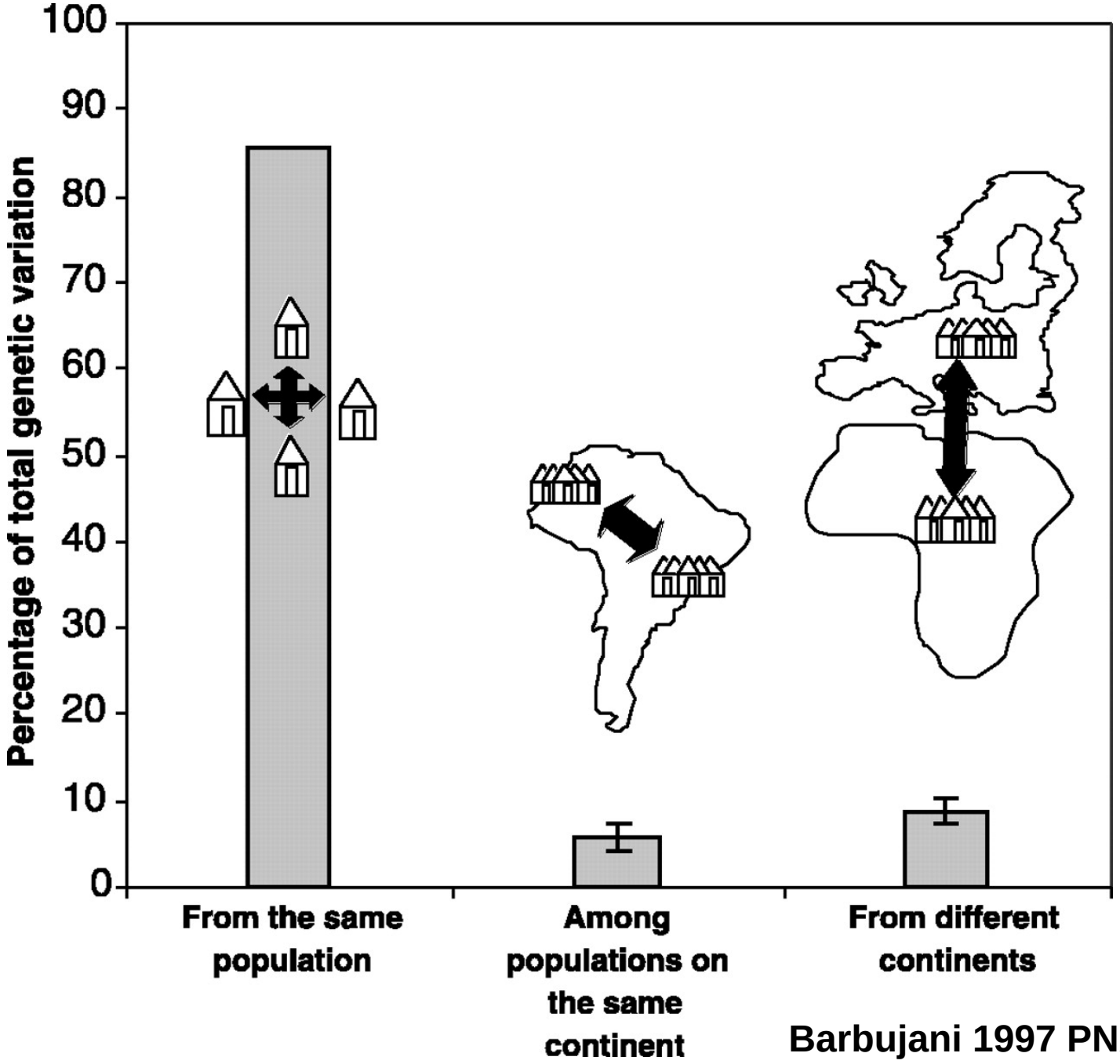

K
Newly Generated Dataset
Comparative Datasets
F
Nilo-Saharan
Chadic
8
7
6
5
4
3
2
2
2
5
8
10
10
10
Southern Africans
Eastern Africans
Central Africans
Western Africans
Northern Africans
Yemenites
African Americans
CEPH-HGDP
Australians
Indians


Mozabite
Dogon
Mandinka
Nigeria AA
Chad NS
Beja
Sudan NS
CAR NK
Ethiopia AA
Ivory Coast NK
Ghana NK
Nigeria NK
CAR
Pygmies
Mbuti
DRC NK
Rwanda NK
Baggara
Northern
Cameroon
(AA, NK, NS)
Fulani
Cameroon
Pygmies
Southern
Cameroon
NK
Southern
Africa
Khoesan
Cape Mixed
Ancestry
Southern
Africa NK
Kenya NS
Kenya AA
Luo
Kenya NK
Hadza
Tanzania NS
Sandawe
Mbugu
Tanzania
AA
Tanzania
NK

A tree based on the genetic distances between the inferred ancestral populations. Differences within Africa can be on the order of differences in the rest of the world.







Barbujani 1997 PNAS 94:4516

Adult Lactose Tolerance in East Africa

Floyd A. Reed (MPI Plön)

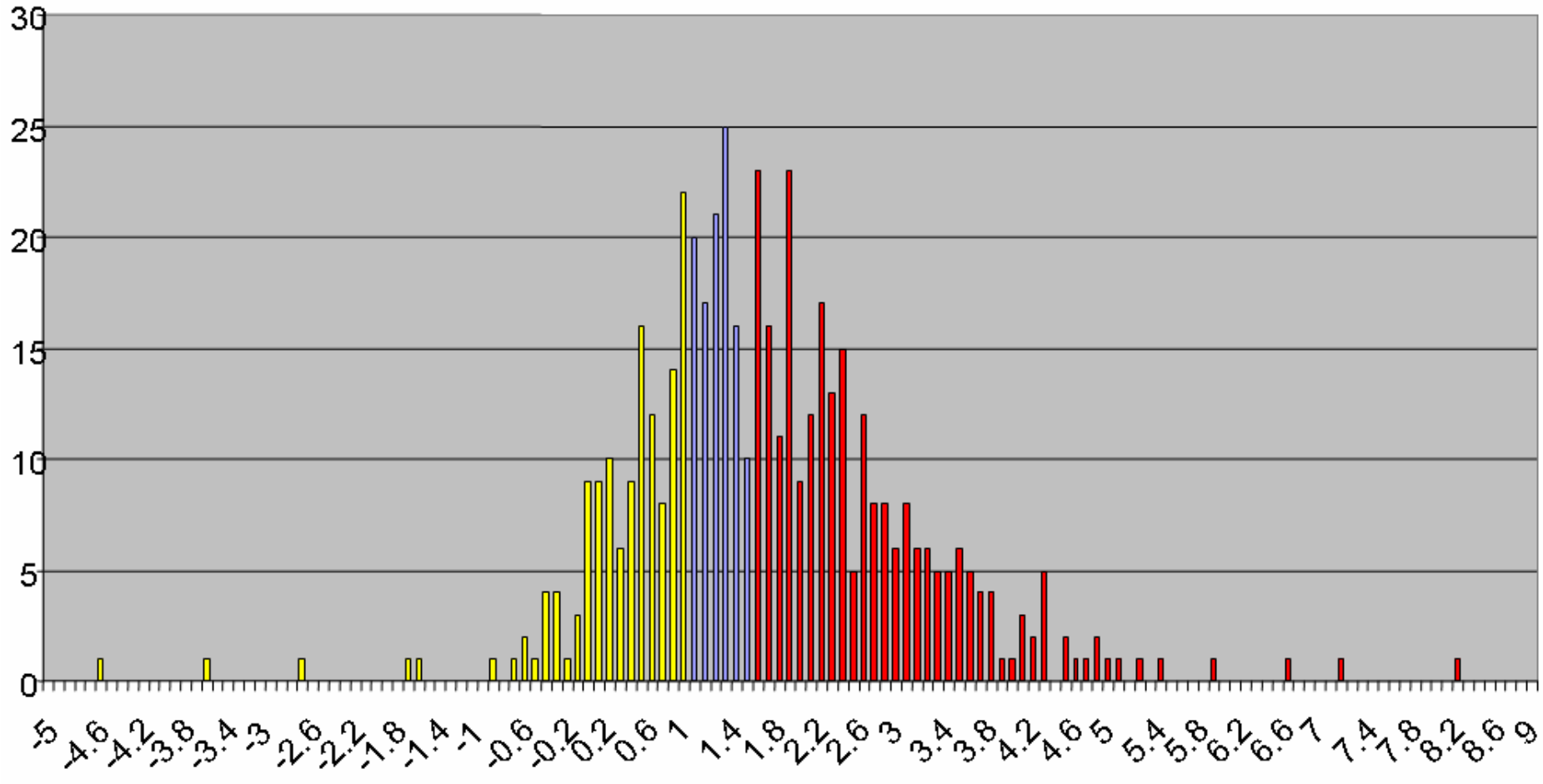
University of Maryland, College Park

The ability to digest milk as adults is a Mendelian inherited trait in Europeans, and is caused by a mutation (T -13910) that has undergone strong positive selection within the last 10,000 years (*e.g*. Bersaglieri *et al*. 2004).

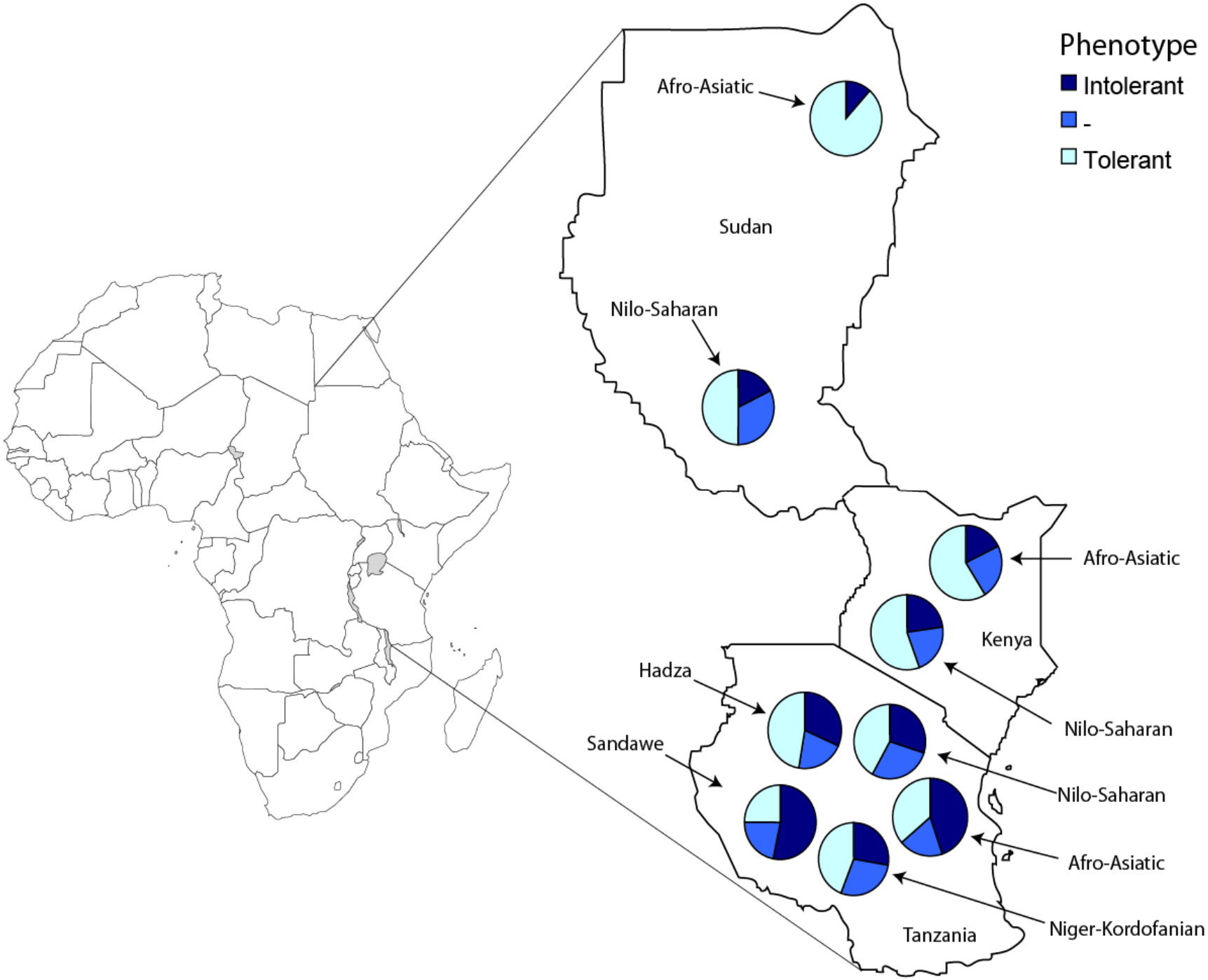
Curiously, many African populations can digest milk as adults but do not have the mutation common in Europeans (Mulcare *et al*. 2004).


EVOLUTION ONE

Phenotype distribution of lactase persistence
N = 470 individuals from Tanzania, Kenya, Sudan

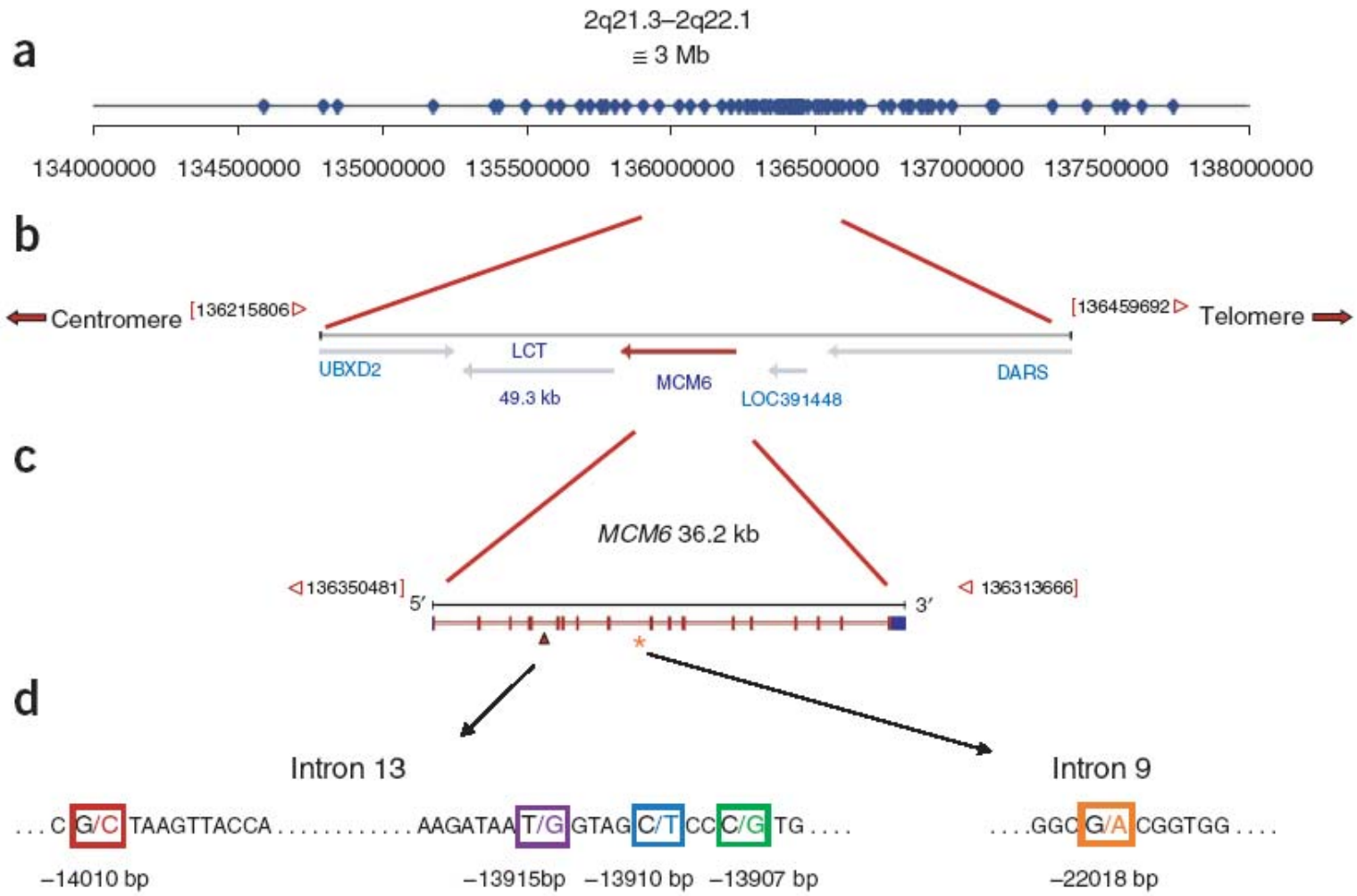


Glucose rise (mmol/l)

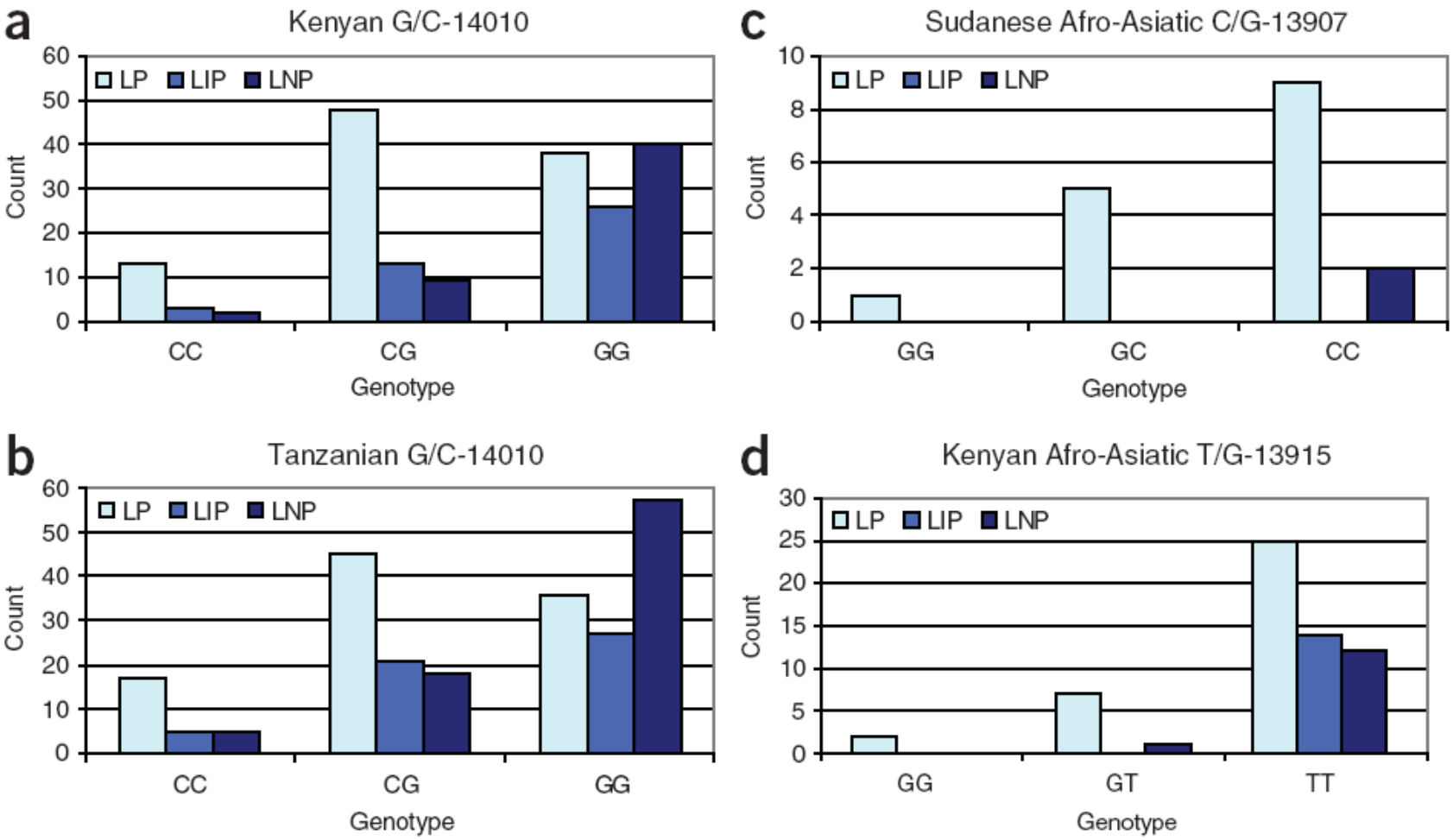

Phenotype
Intolerant
-
Tolerant
Afro-Asiatic
Sudan
Nilo-Saharan
Afro-Asiatic
Kenya
Nilo-Saharan
Hadza
Sandawe
Nilo-Saharan
Afro-Asiatic
Niger-Kordofanian
Tanzania

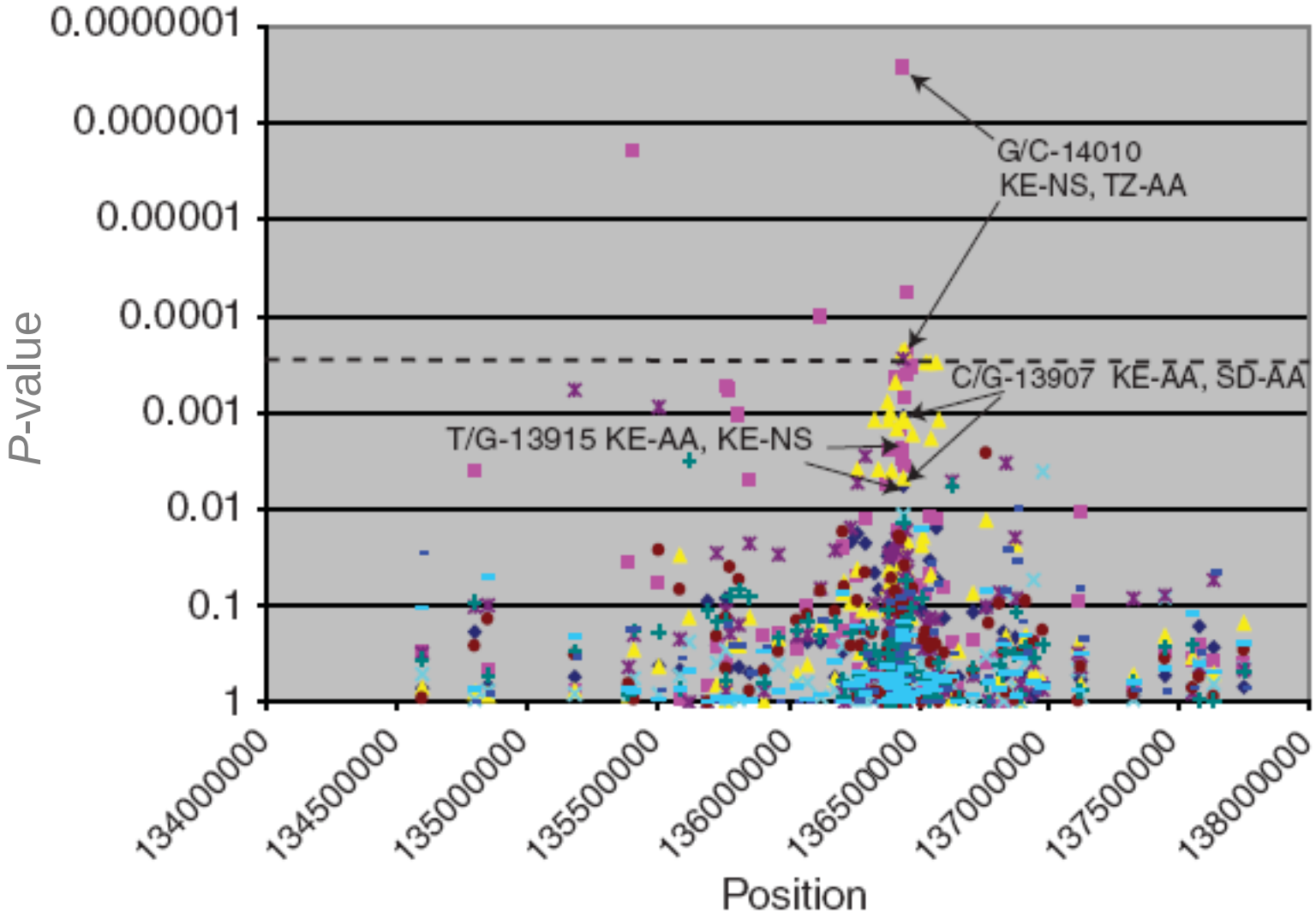
gDNA sample collection, Maasai, Tanzania

Three new SNPs near the regulatory site identified in Europeans are identified by resequencing.

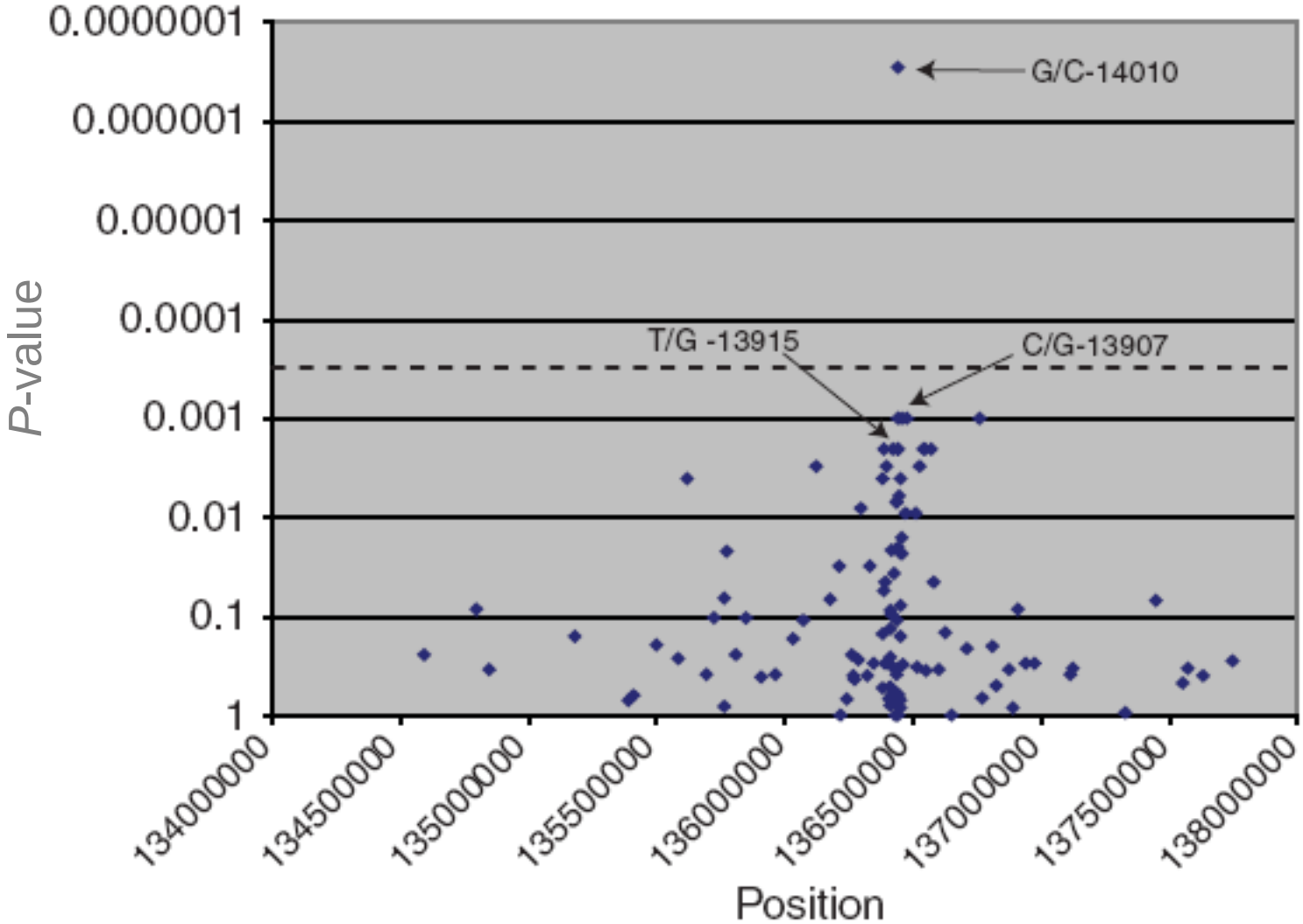


Genotype-Phenotype Associations

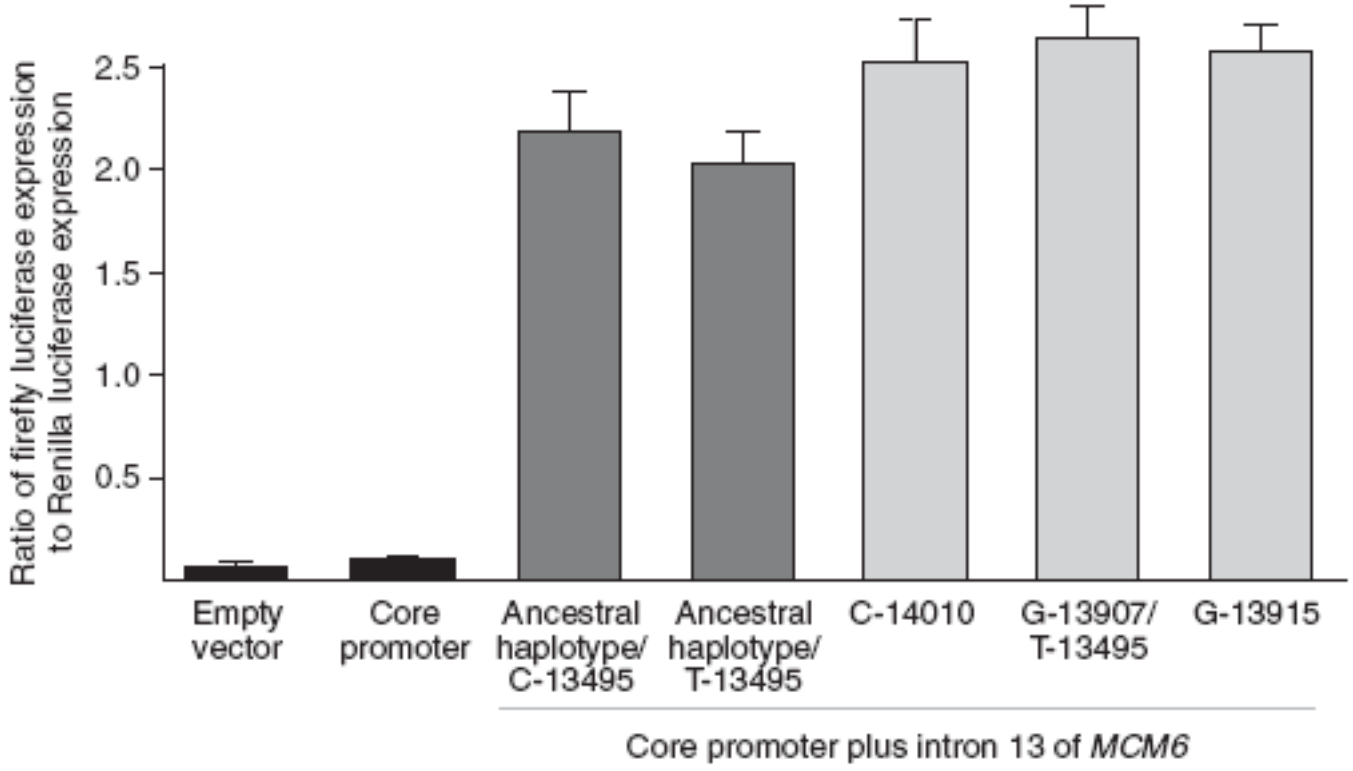



0.0000001
0.000001
0.00001
0.0001
0.001
0.01
0.1
1
P-value
G/C-14010
KE-NS, TZ-AA
C/G-13907 KE-AA, SD-AA
T/G-13915 KE-AA, KE-NS
134000000
134500000
135000000
135500000
136000000
136500000
137000000
137500000
138000000
Position

G/C -14010 is significantly associated with the phenotype.

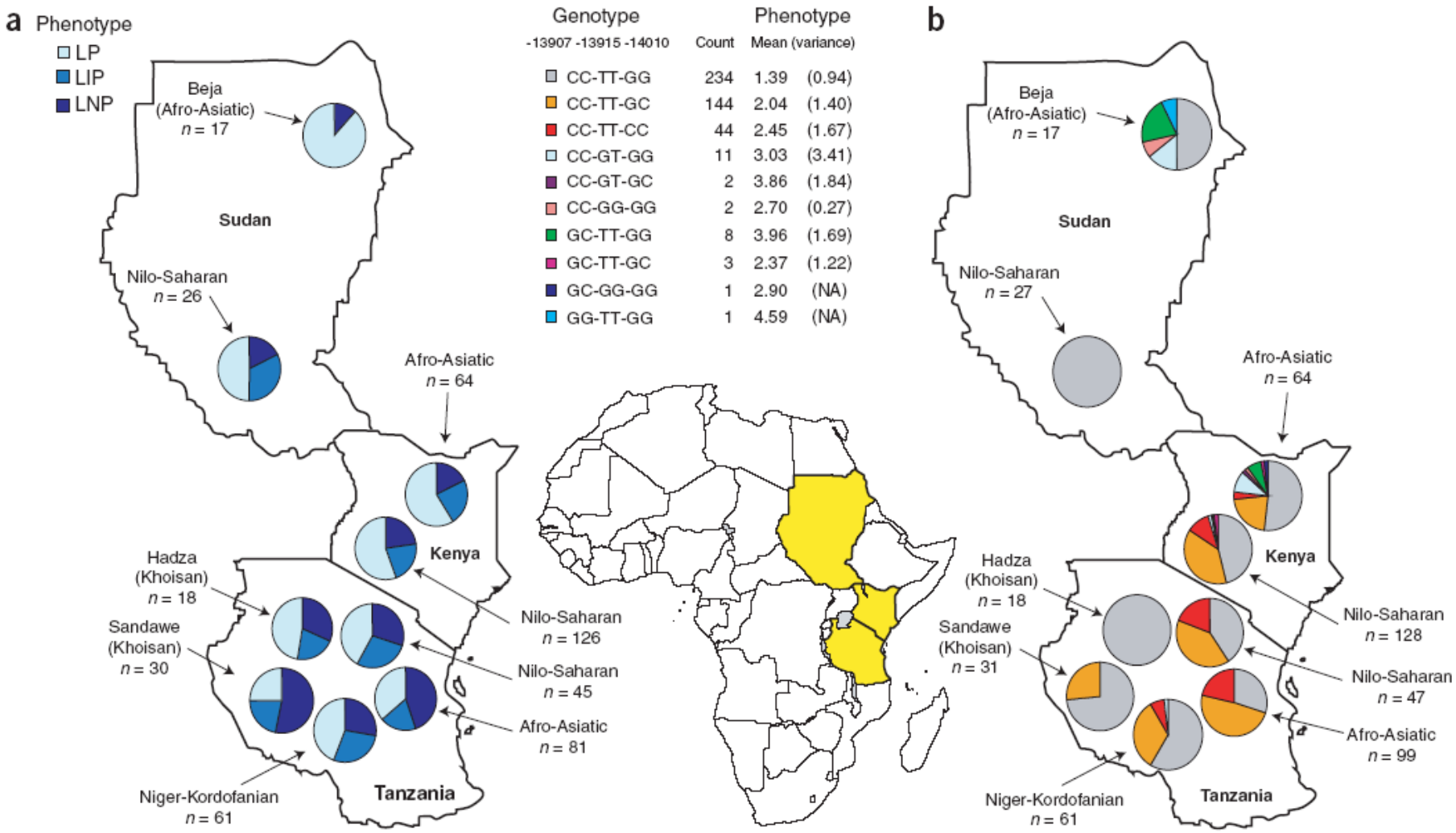


These three SNPs resulted in a significant increase in expression *in vitro*.

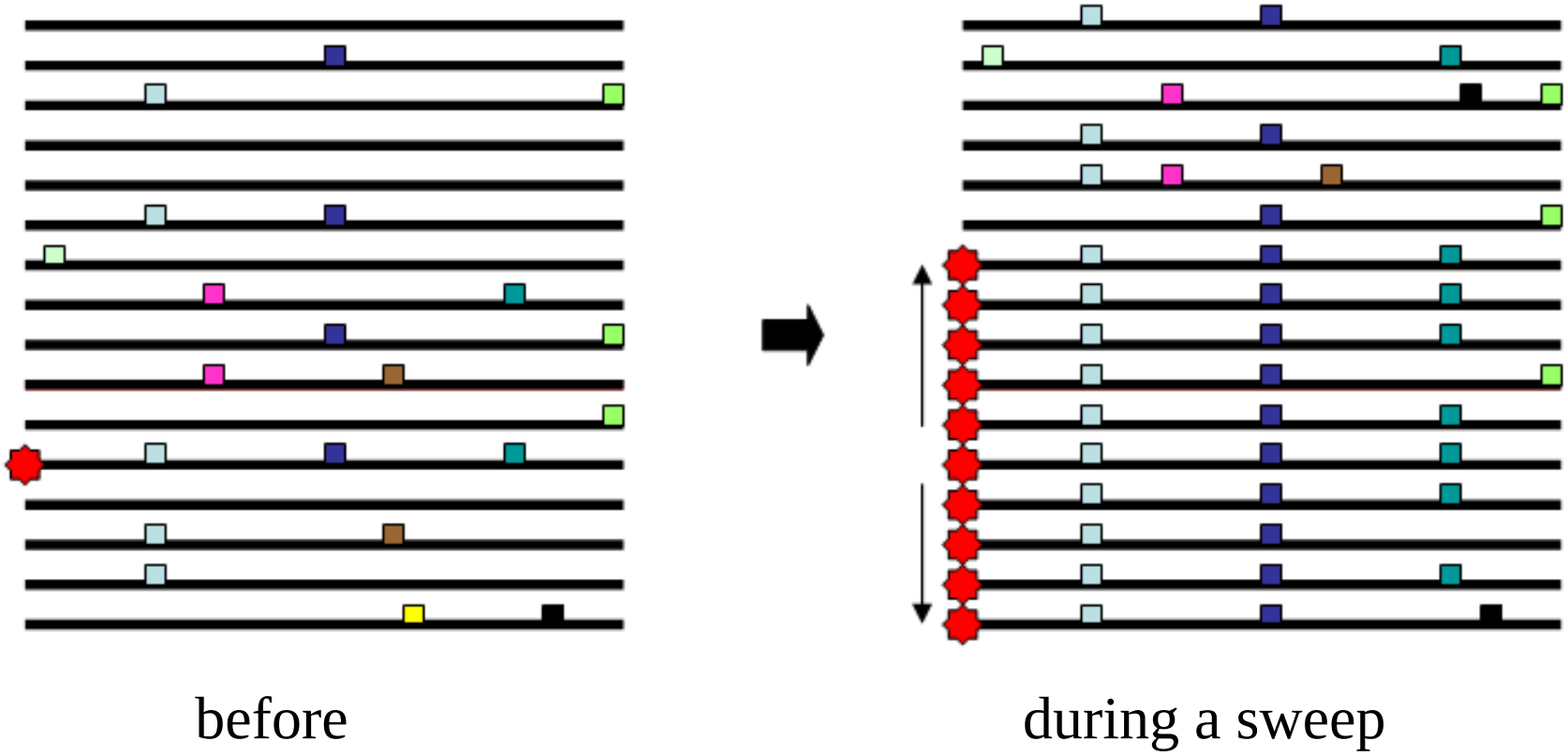


Babbitt, Wray, Duke U.

One of these alleles, G/C -14010, is at a very high frequency in E. Africa

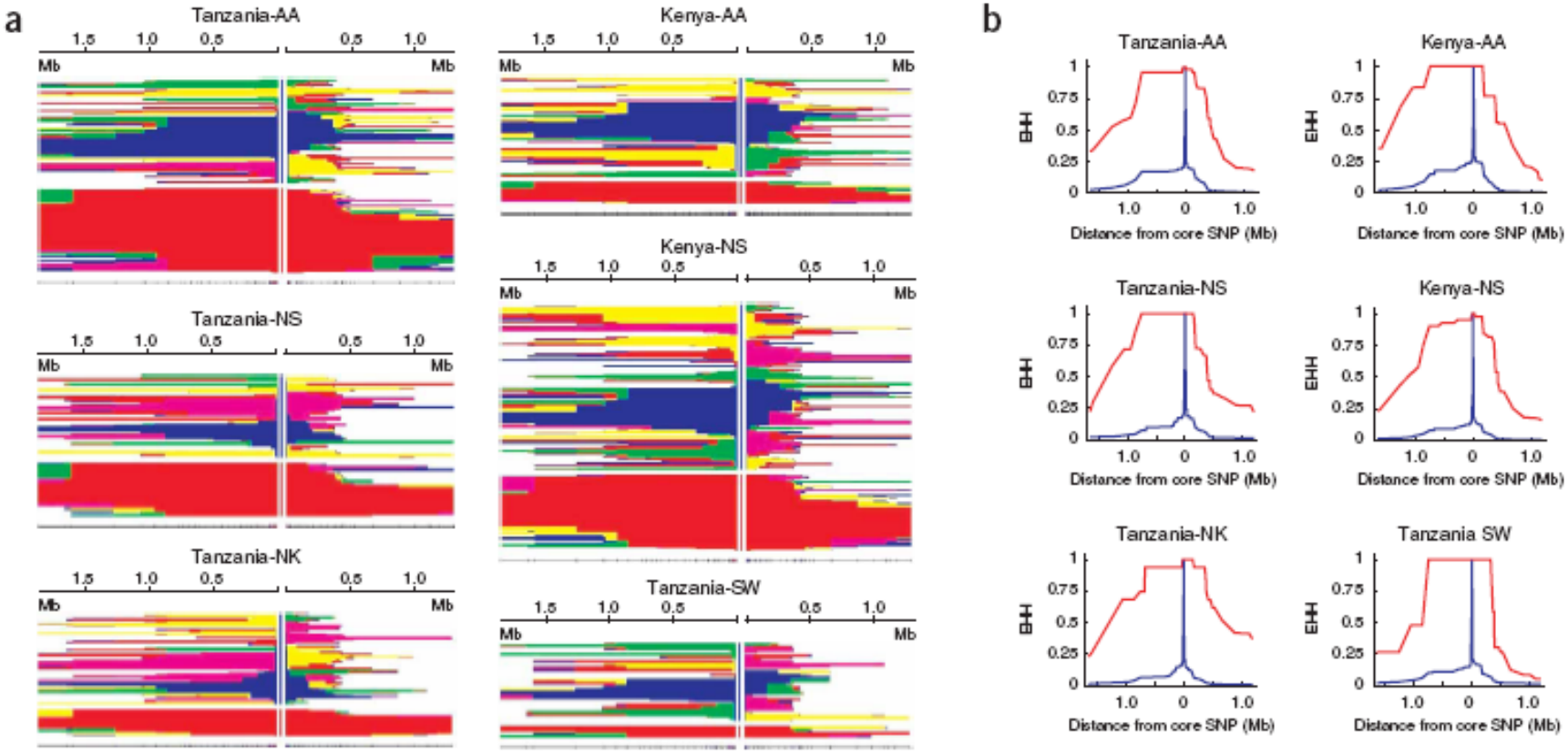


Partial selective sweep/hitchhiking



Genetic variation along a region of a chromosome can be carried to higher frequency by positive selection.

The decay of haplotype homozygosity around the -14010 allele

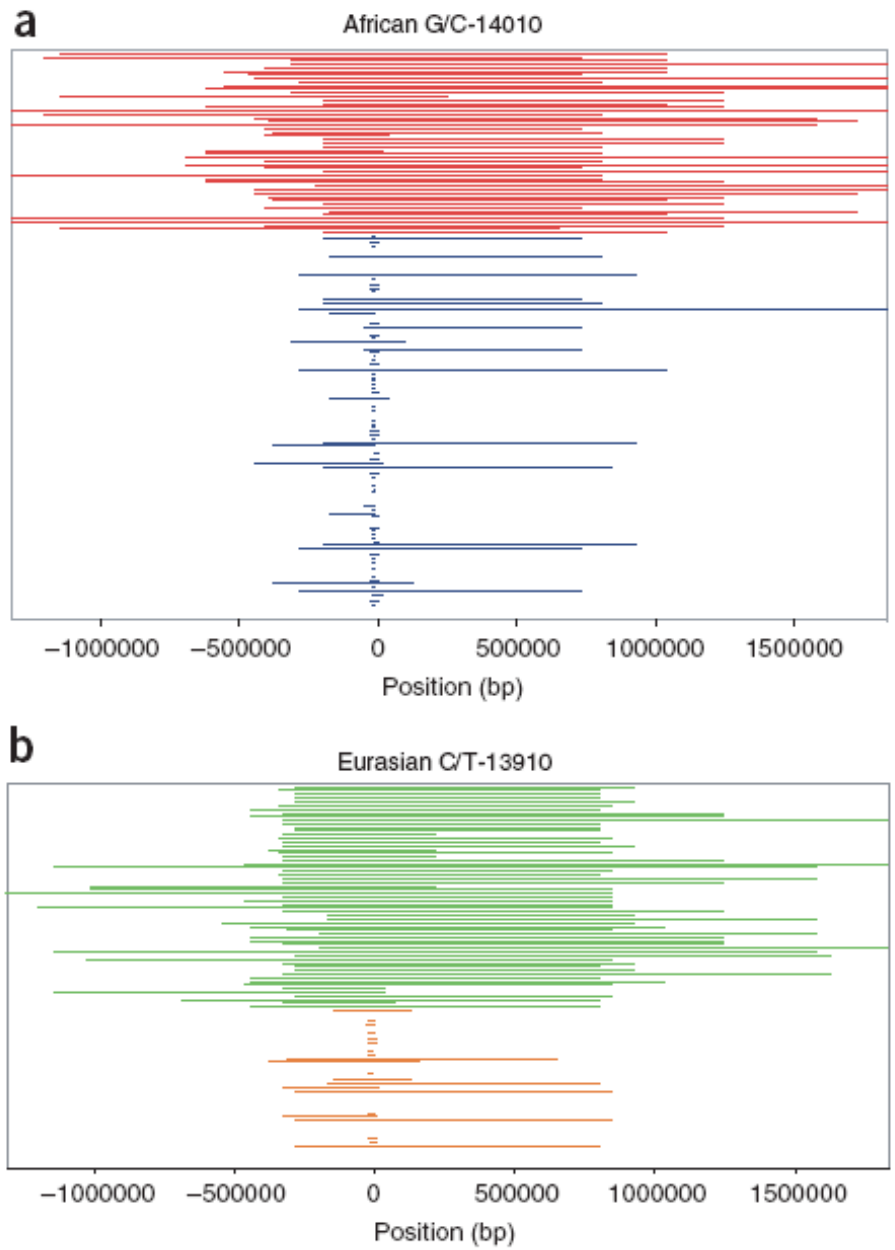


The combination of low variation on one high frequency haplotype background and high variation on alternative backgrounds is unexpected without invoking recent positive selection.

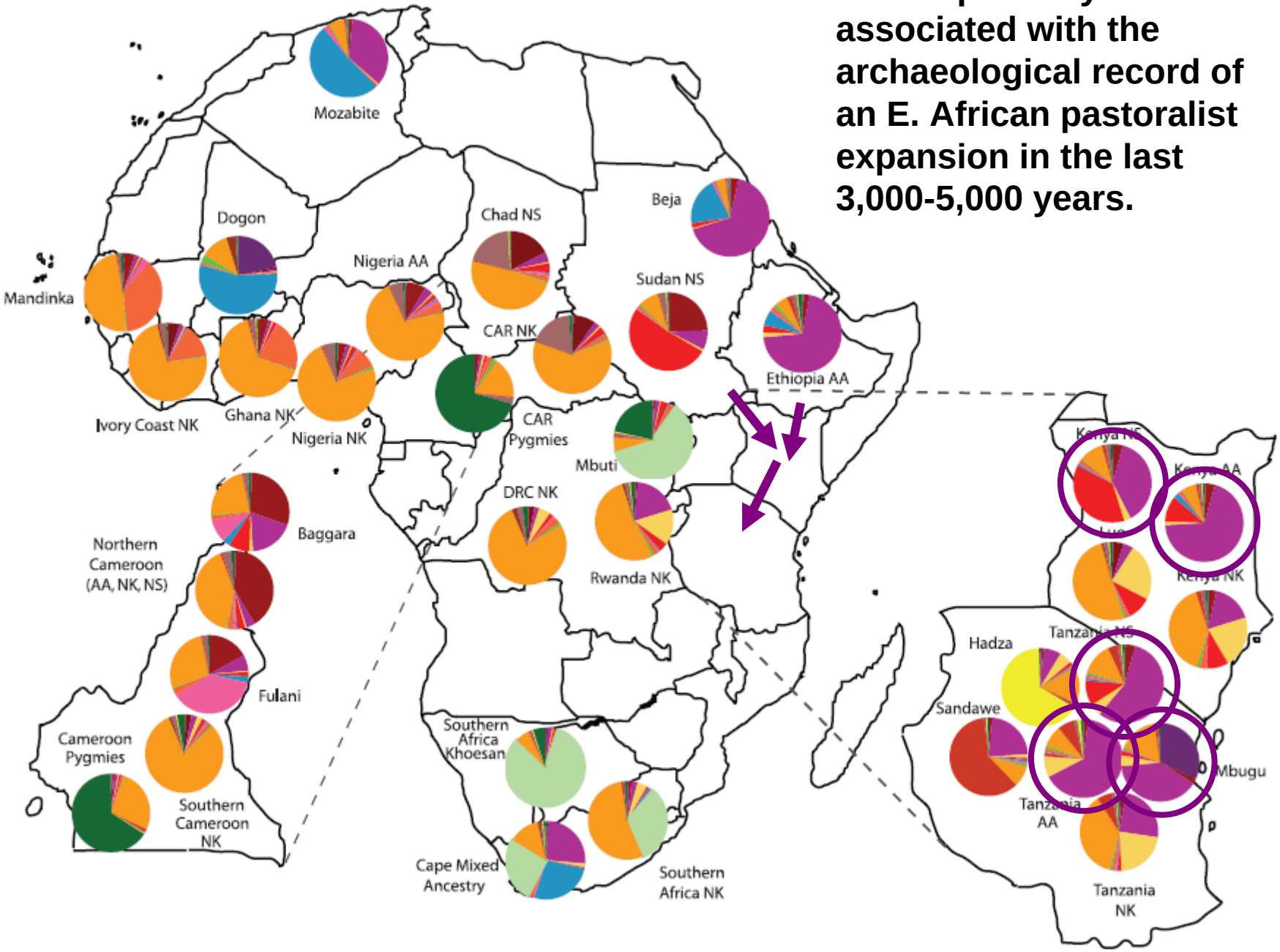
Voight, Pritchard, U. Chicago

The extent of haplotype homozygosity suggests strong recent positive selection (a 7% fitness advantage over 3-6,000 years).

The oldest age estimate is for the Sandawe sample (~6-7,000 years)?

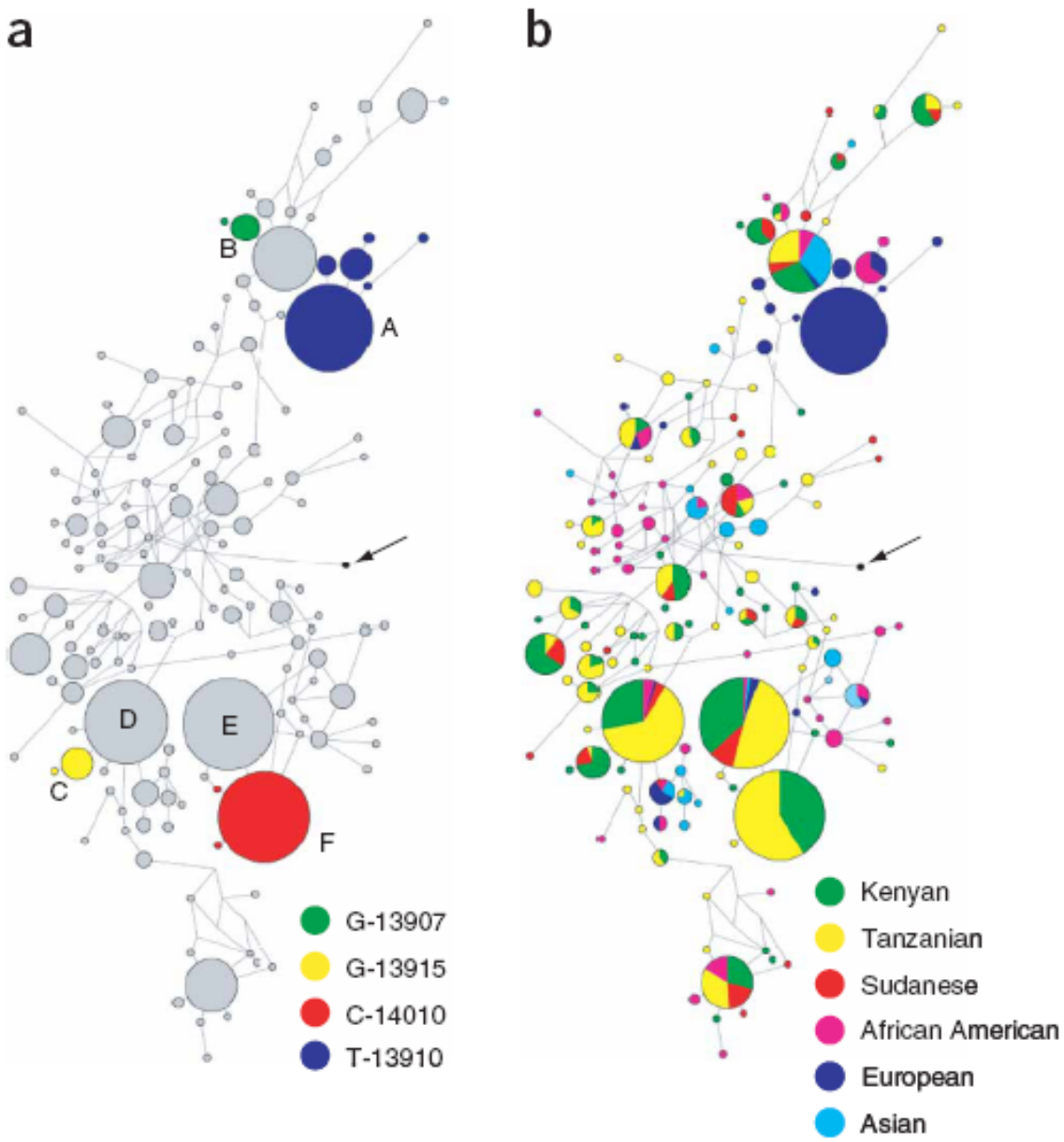


This is possibly associated with the archaeological record of an E. African pastoralist expansion in the last 3,000-5,000 years.

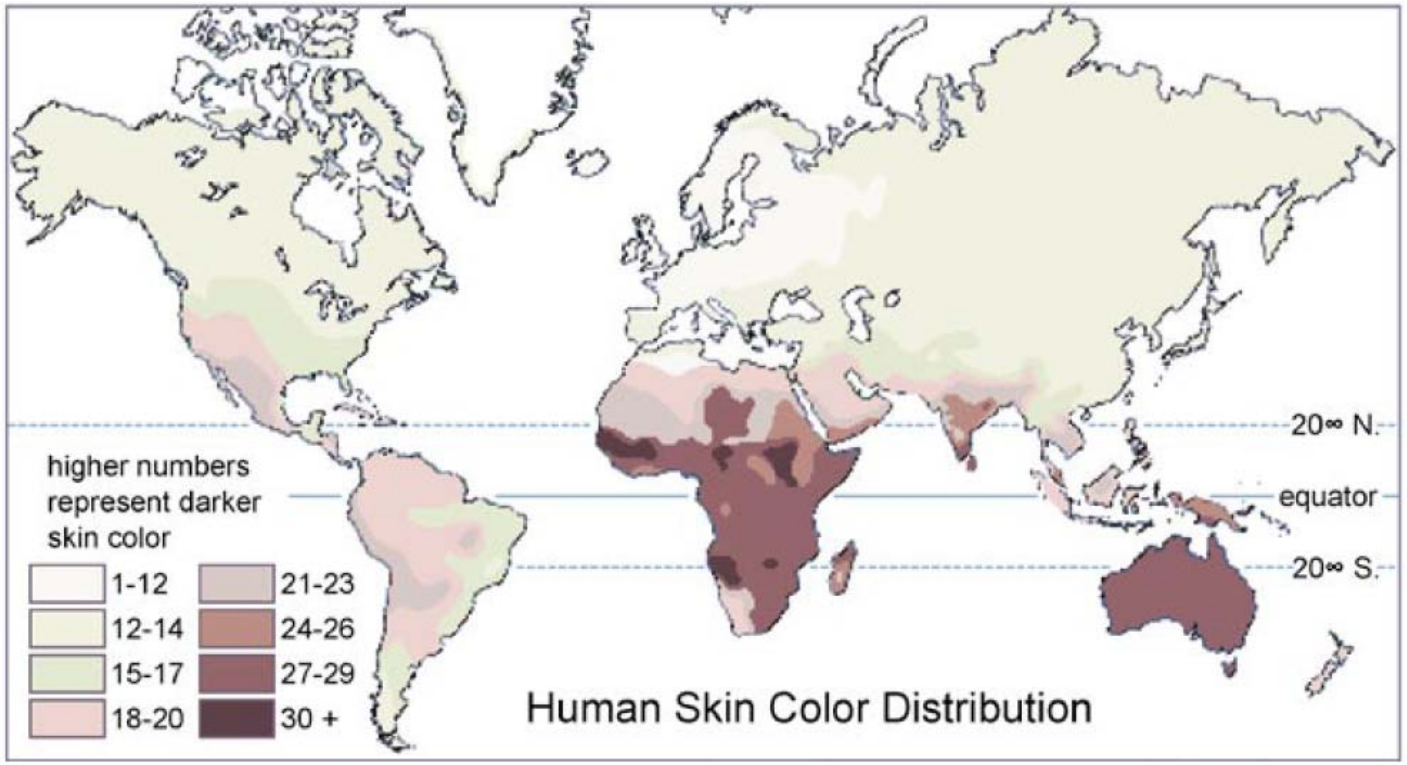


Haplotype Network

These adaptive mutations originated on independent haplotype backgrounds



Other examples of parallel adaptation

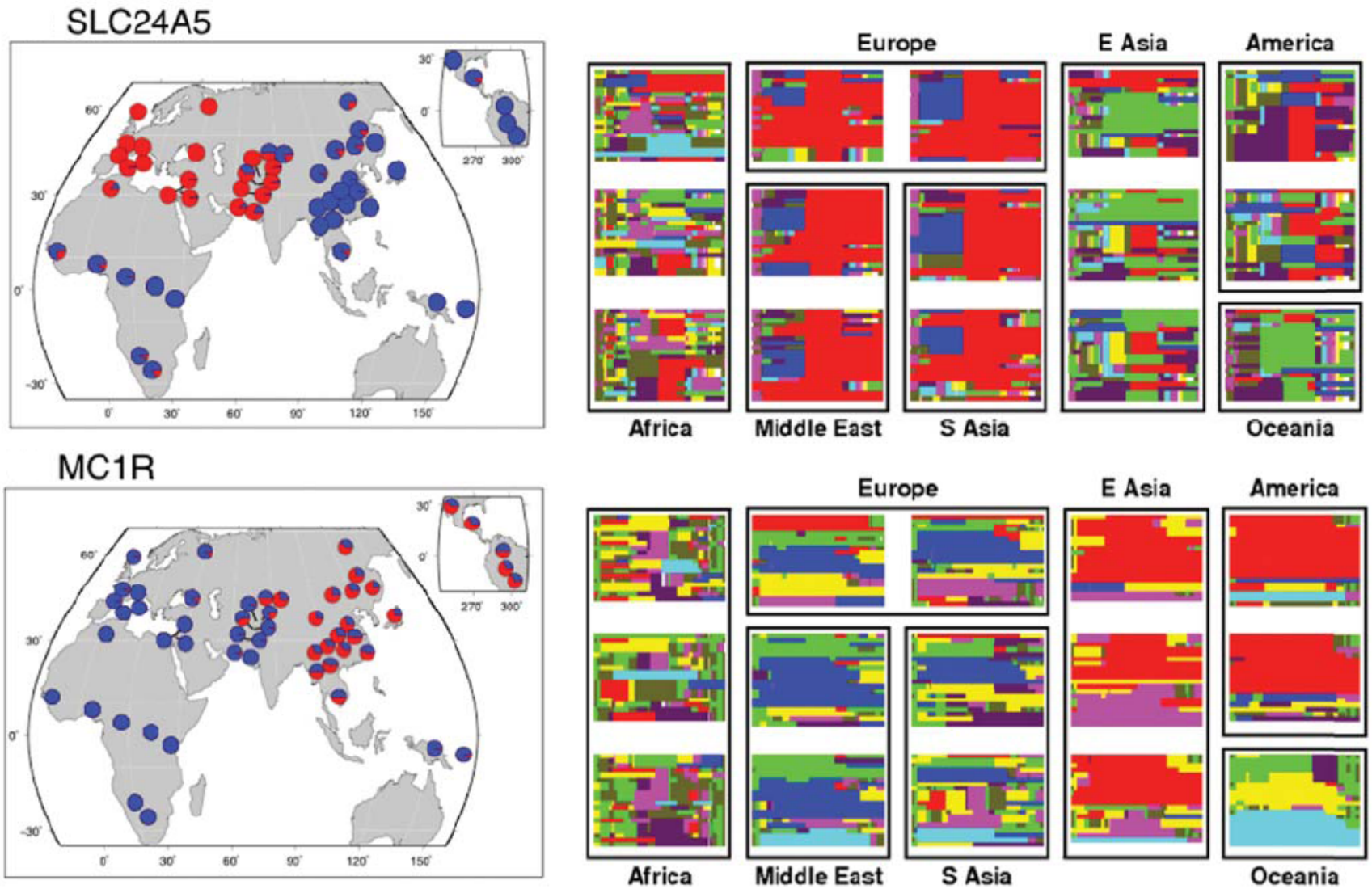


DOI: 10.1371/journal.pbio.0000027.g002

Barsh 2003 PLoS Bio. 1:019

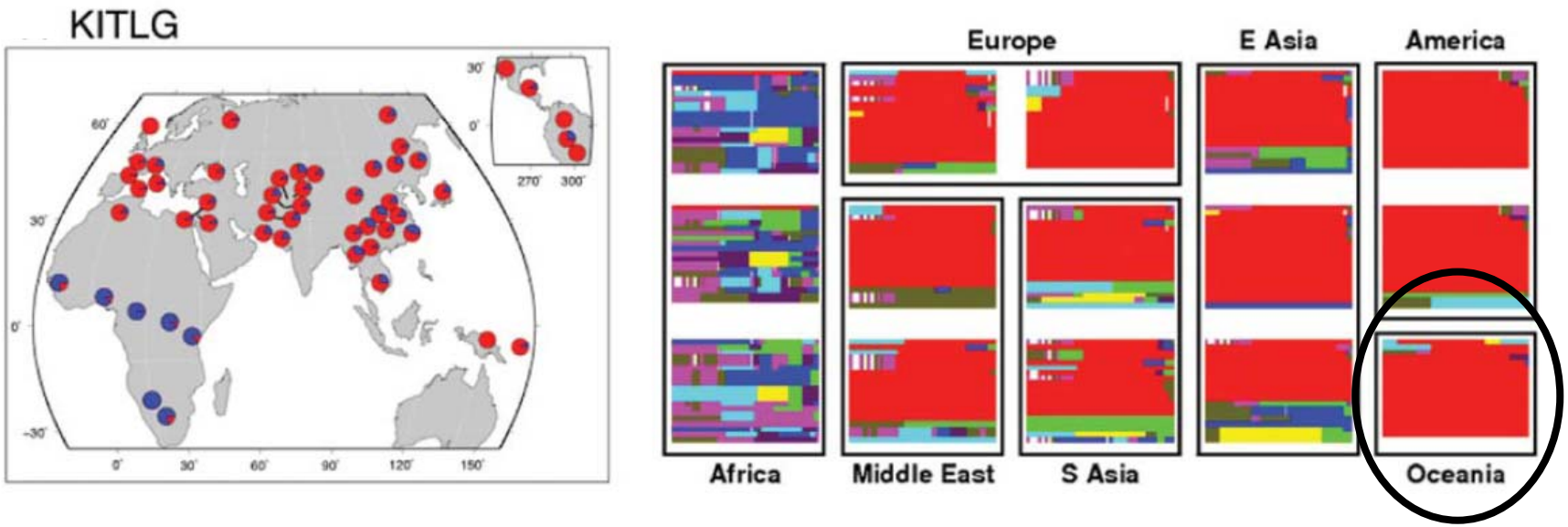
European and East Asian populations have light skin coloration but different sets of alleles at different genes seem to be responsible (Norton et al. 2007, Mol. Biol. Evol. 24: 710-722)

Other examples of regional positive selection



Coop et al. 2009 PLoS Genetics 5:e1000500

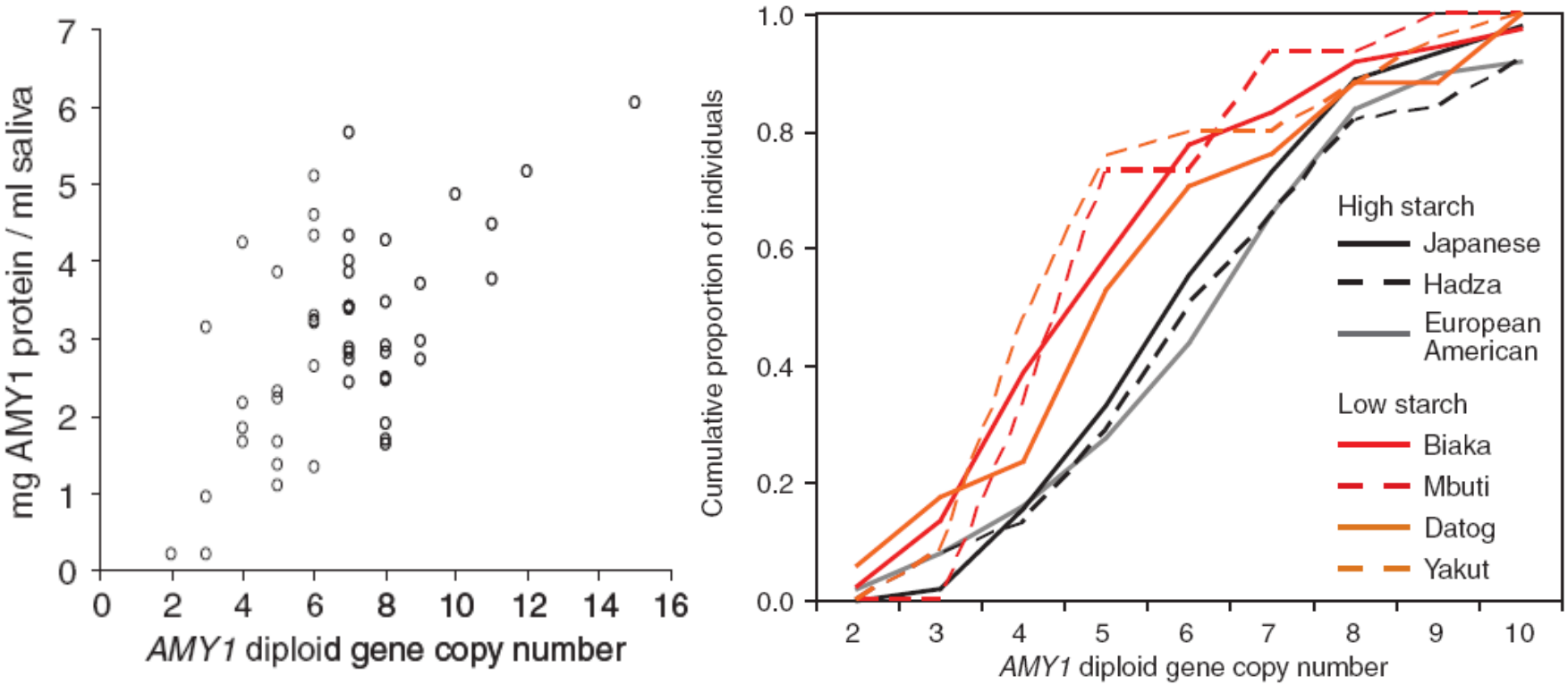
Not a simple story…



Oceanic populations can have very dark pigmentation.

Coop et al. 2009 PLoS Genetics 5:e1000500

Another example of adaptive gene-culture coevolution, *AMY1*.



AMY1 copy number is correlated with amylase protein concentration in the saliva. Copy number is also correlated with the amount of starch in a populations diet.

Perry et al. 2007 Nat. Genet. 39:1256

Additional questions

Other loci?

Other populations?

Role in hunter-gatherers? (starch diets and phlorizin)

Form of the selective advantage and how it was established?

In Europe adult lactose tolerance may have evolved in response to low levels of sunlight and low dietary levels of vitamin D. A principle role of vitamin D is in calcium absorption. Milk provides calcium and lactose promotes the uptake of calcium (Flatz and Rotthauwe 1973, Lancet 302:76-77).

What was the selective force for lactose tolerance in East Africa?

-- simply to take advantage of the added nutrition from milk?

-- or to use milk as a water source? (Milk is a sufficient source of water for newborns and perhaps also allows contaminated water to be avoided.)

Portions of East Africa are very arid.

Most mammals can go for longer periods without water than humans (domesticated cattle for twice as long).

If human populations could exploit water sources from domesticated mammals, this could have given an advantage in surviving and exploring arid environments.

However, in people that are lactose intolerant, water loss can be dramatically increased when milk is consumed, which suggests it is difficult for the cultural-genetic trait to increase when rare.

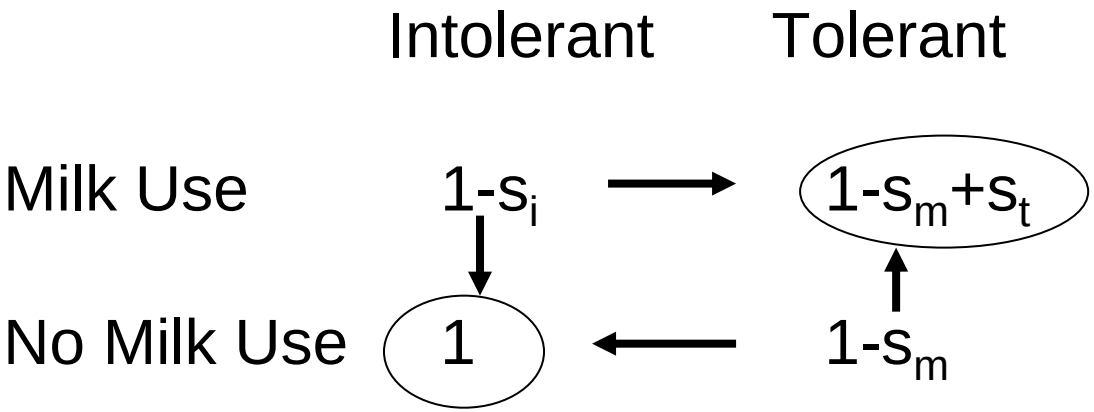
Fitness in an arid environment

	Intolerant	Tolerant
Milk Use	$1-s_i$	$1-s_m+s_t$
No Milk Use	1	$1-s_m$

s_m is small
s_i and s_t are large

This suggests a bi-stable dynamic

Fitness in an arid environment



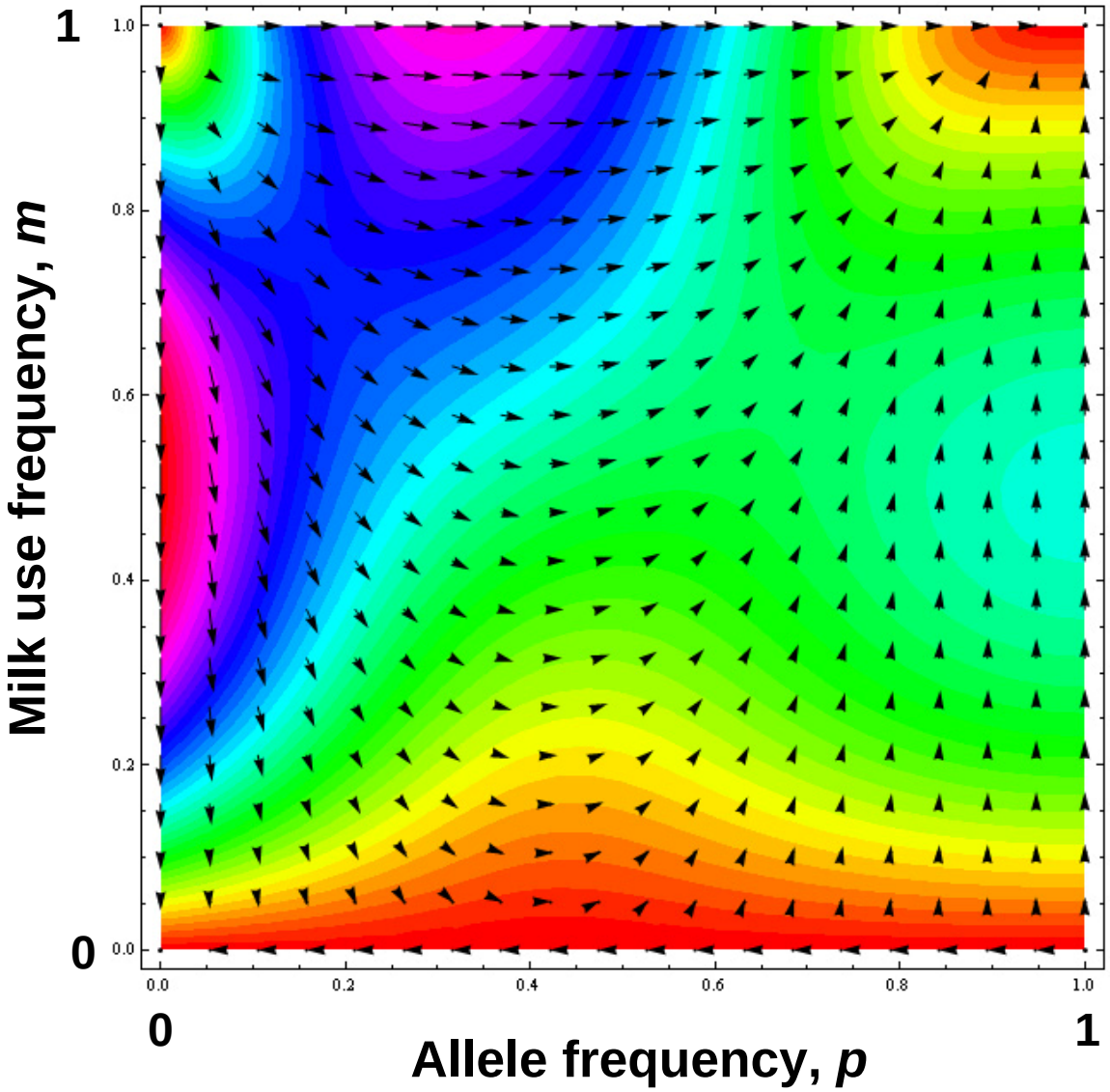
s_m is small
s_i and s_t are large

In a population an allele is expected to change in frequency according to its average fitness.

$$p' = \frac{f_p p}{\overline{w}}$$

We can think of the spread of a cultural trait in a similar fashion.

$$m' = \frac{f_m m}{\overline{w}}$$



s_i=-0.1
s_t=0.05
s_m=-0.001

Methods exist to process milk to reduce the lactose content; cheese, kefir, yogurt… , but this also reduces the water content and takes time to process.)

What if an alternative water source were available for lactose intolerant individuals?

Cattle milk ~87% water
Cattle blood ~50% water


http://dicksandy.org/Travel/HTML/TanzaniaHTM/Maramboi.ht


http://dicksandy.org/Travel/HTML/TanzaniaHTM/Maramboi.ht

http://www.worldofstock.com/closeups/PCU5033.php

Fitness in an arid environment

Without blood alternative:

	Intolerant	Tolerant
Milk Use	$1-s_i$	$1-s_m+s_t$
No Milk Use	1	$1-s_m$

With blood alternative:

	Intolerant	Tolerant
Milk/Blood Use	$1+s_b$	1-sm+st
No Milk Use	1	1-sm

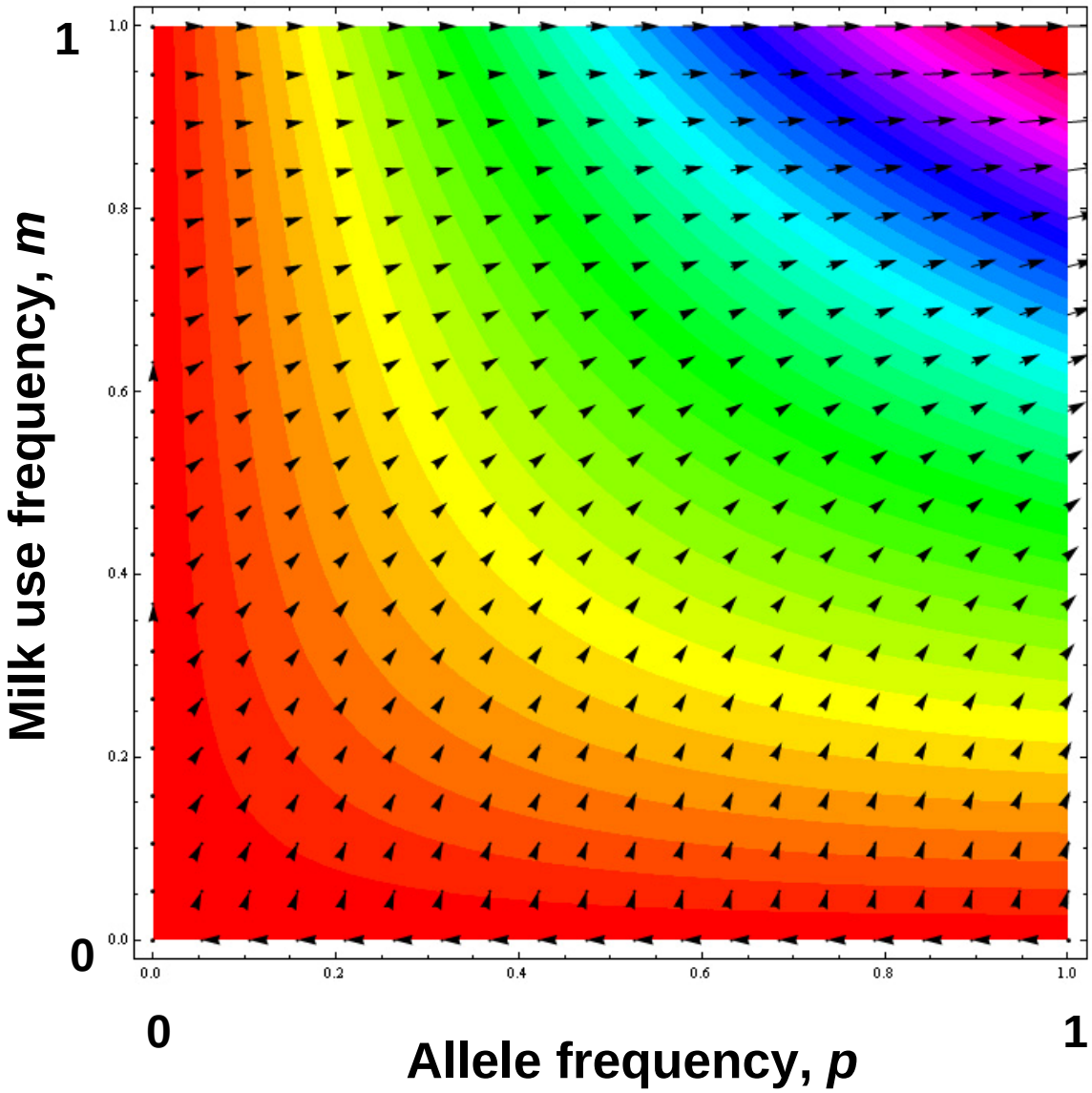
Fitness in an arid environment

Without blood alternative:

	Intolerant	Tolerant
Milk Use	$1-s_i$	$1-s_m+s_t$
No Milk Use	1	$1-s_m$

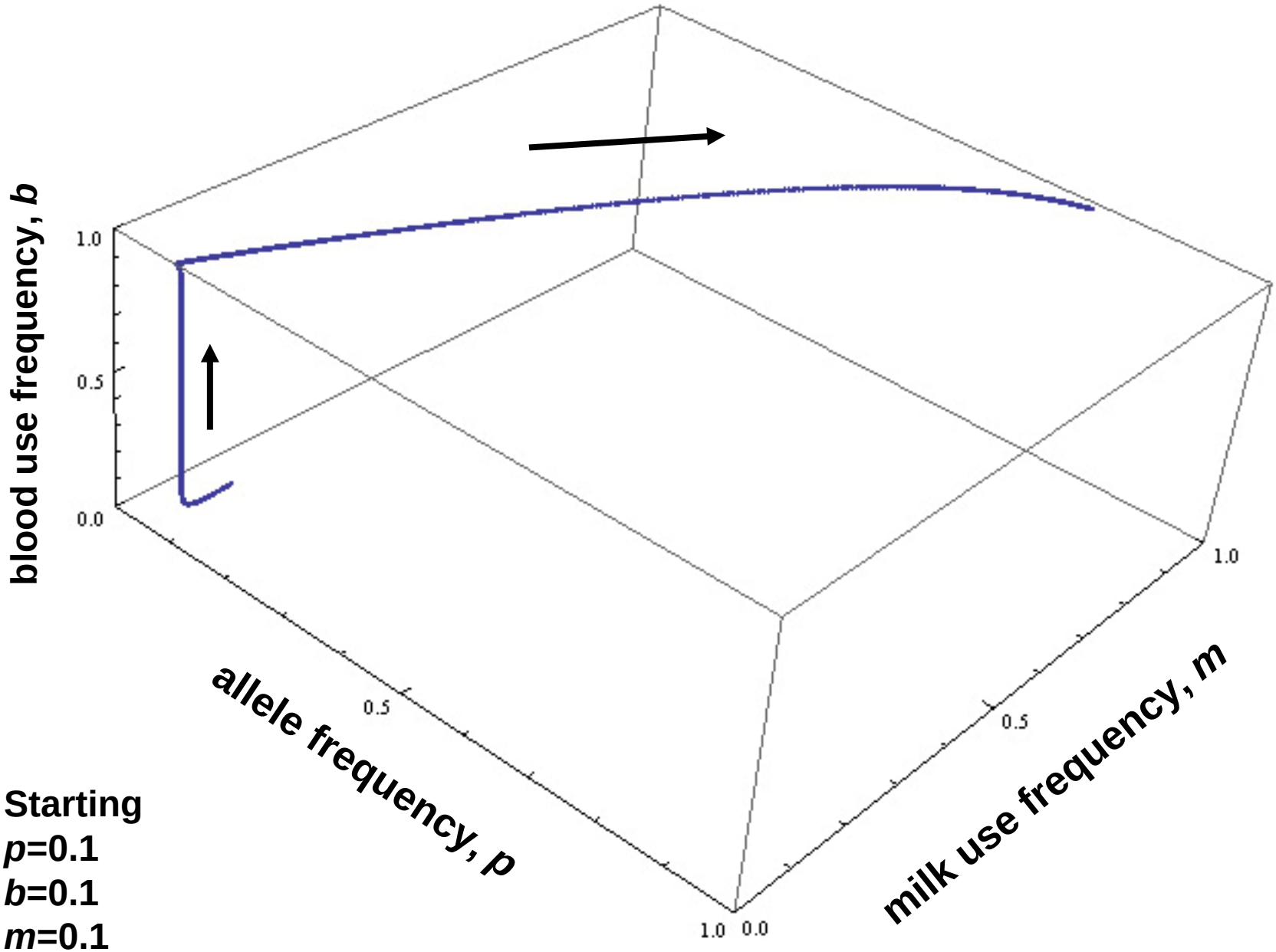
With blood alternative:

	Intolerant	Tolerant
Milk/Blood Use	$1+s_b$	1-sm+st
No Milk Use	1	1-sm



s_i=-0.1
s_t=0.05
s_m=-0.001

s_b=0.01
b=1



Starting
***p*=0.1**
***b*=0.1**
***m*=0.1**

My question: Is it possible that blood can be an alternative water source to milk?

Is ritual blood use among the Maasai a cultural legacy of the transition to milk use?

Other ways to adjust the model

Perhaps one key is to make s_i frequency dependent on *m* (only becomes a large cost when milk use is very common),

have cultural inheritance correlated with genotypes (within a family, people more likely to be tolerant are more likely to rely on milk),

have a two-deme arid/non-arid model,

or the effects of drift in small finite populations?

Acknowledgements

Janne Bondi Johannessen and Eivind Hovig

DNA sample donors and test subjects

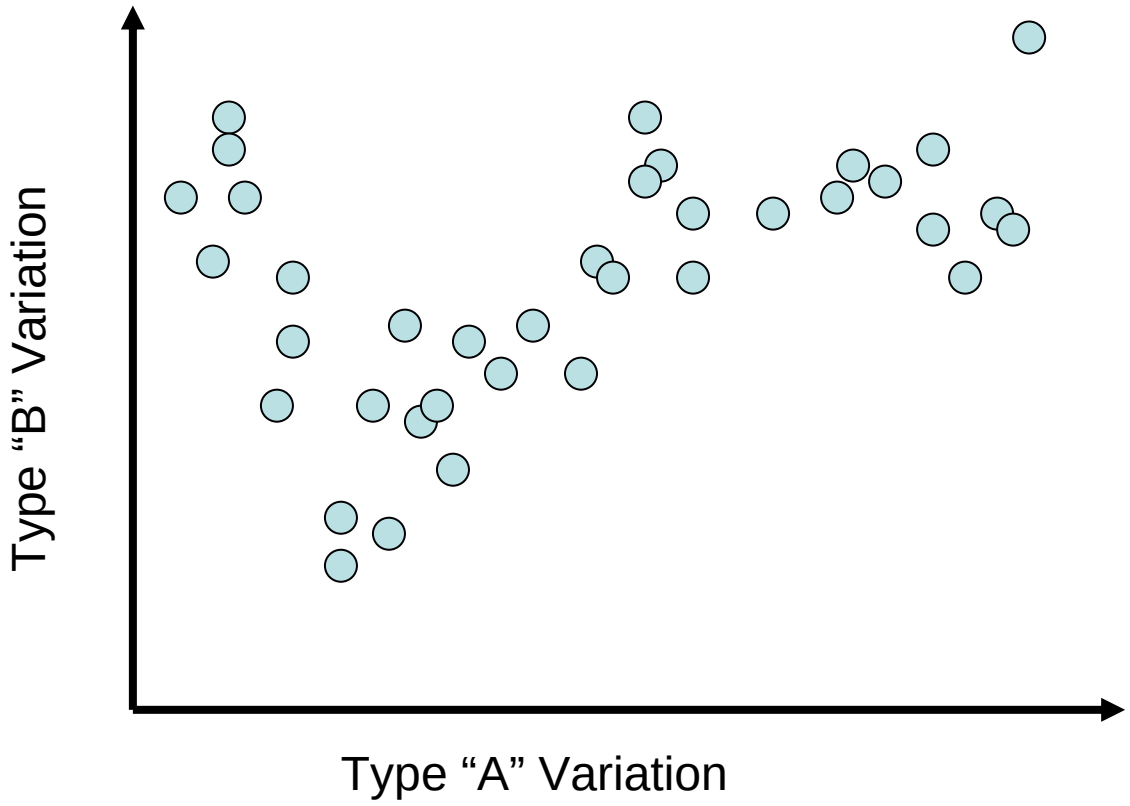
The Tishkoff Lab, U. Maryland/U.Penn. and many collaborators
Sarah Tishkoff,
Alessia Ranciaro,
Jibril Hirbo

Wray Lab, Duke U.

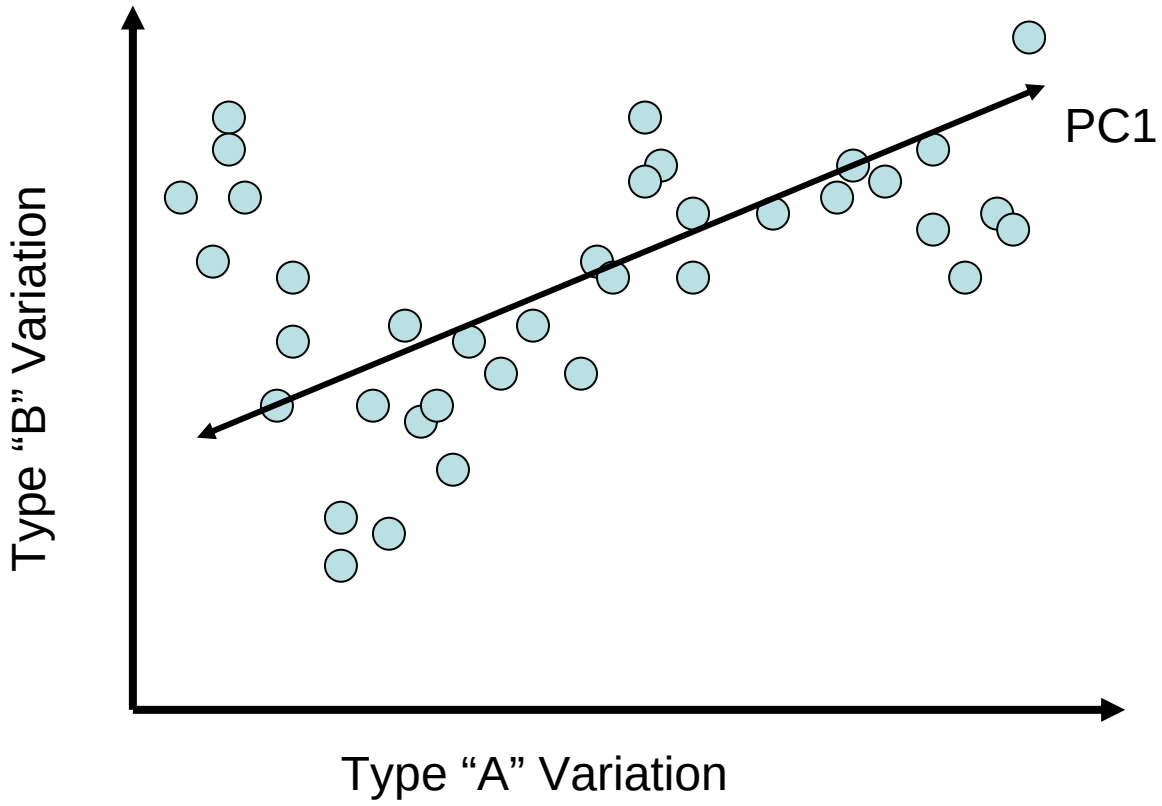
Pritchard Lab, U. of Chicago

The Evolutionary Dynamics Group, MPI Evol. Bio.
Arne Traulsen
Philipp Altrock
Chaitanya Gokhale

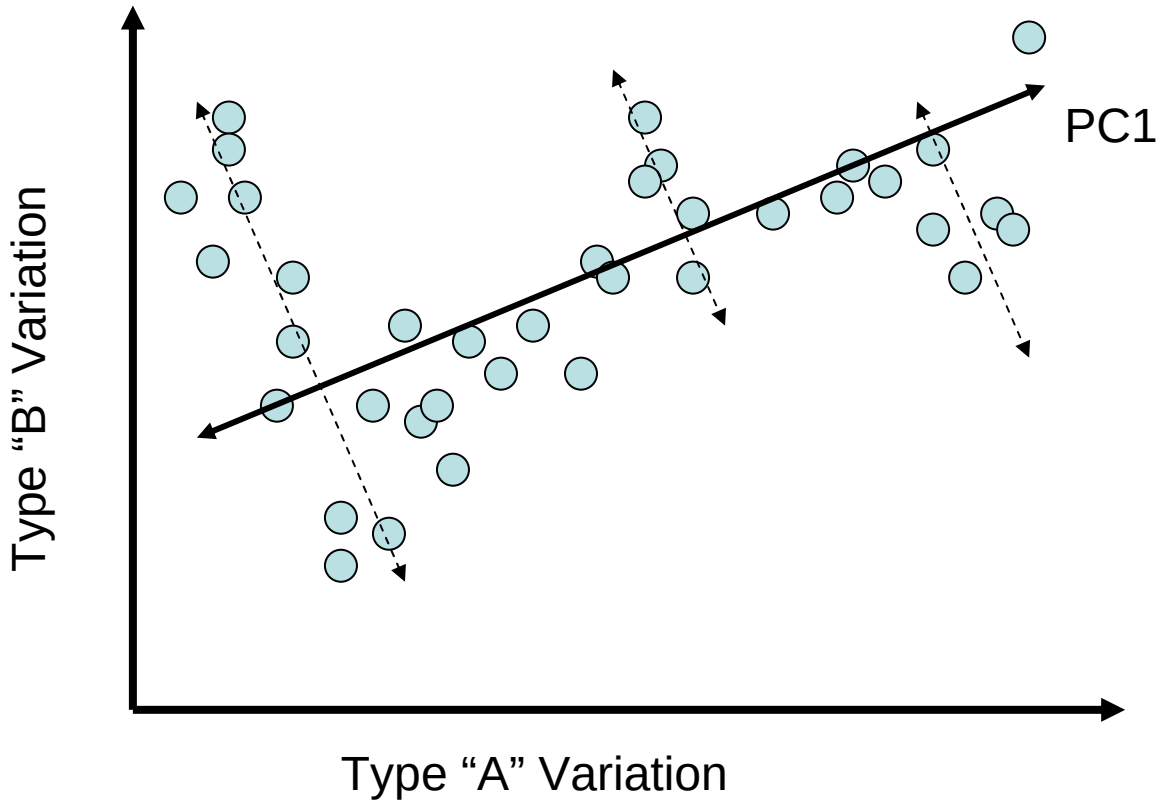
Principle Components can describe complex datasets in terms of simpler uncorrelated axes that represent as much variation as possible.



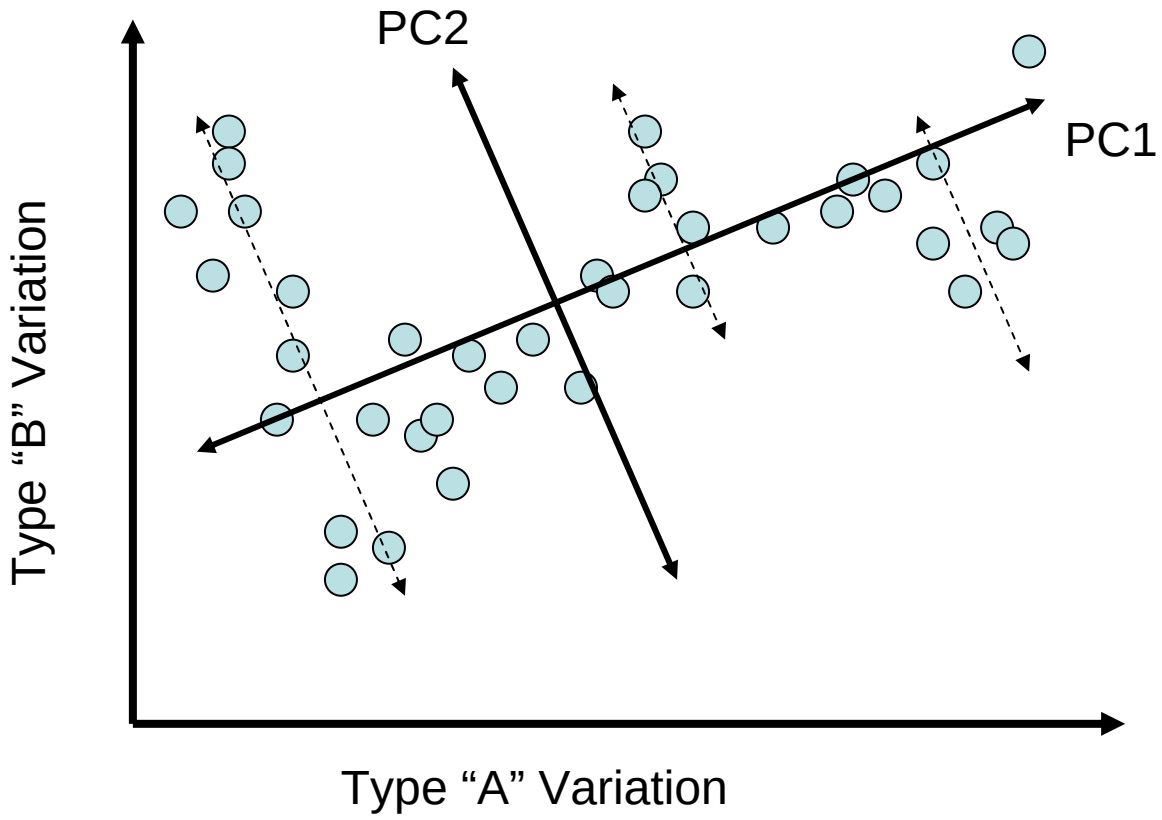
Principle Components can describe complex datasets in terms of simpler uncorrelated axes that represent as much variation as possible.



Principle Components can describe complex datasets in terms of simpler uncorrelated axes that represent as much variation as possible.



Principle Components can describe complex datasets in terms of simpler uncorrelated axes that represent as much variation as possible.




http://dicksandy.org/Travel/HTML/TanzaniaHTM/Maramboi.ht