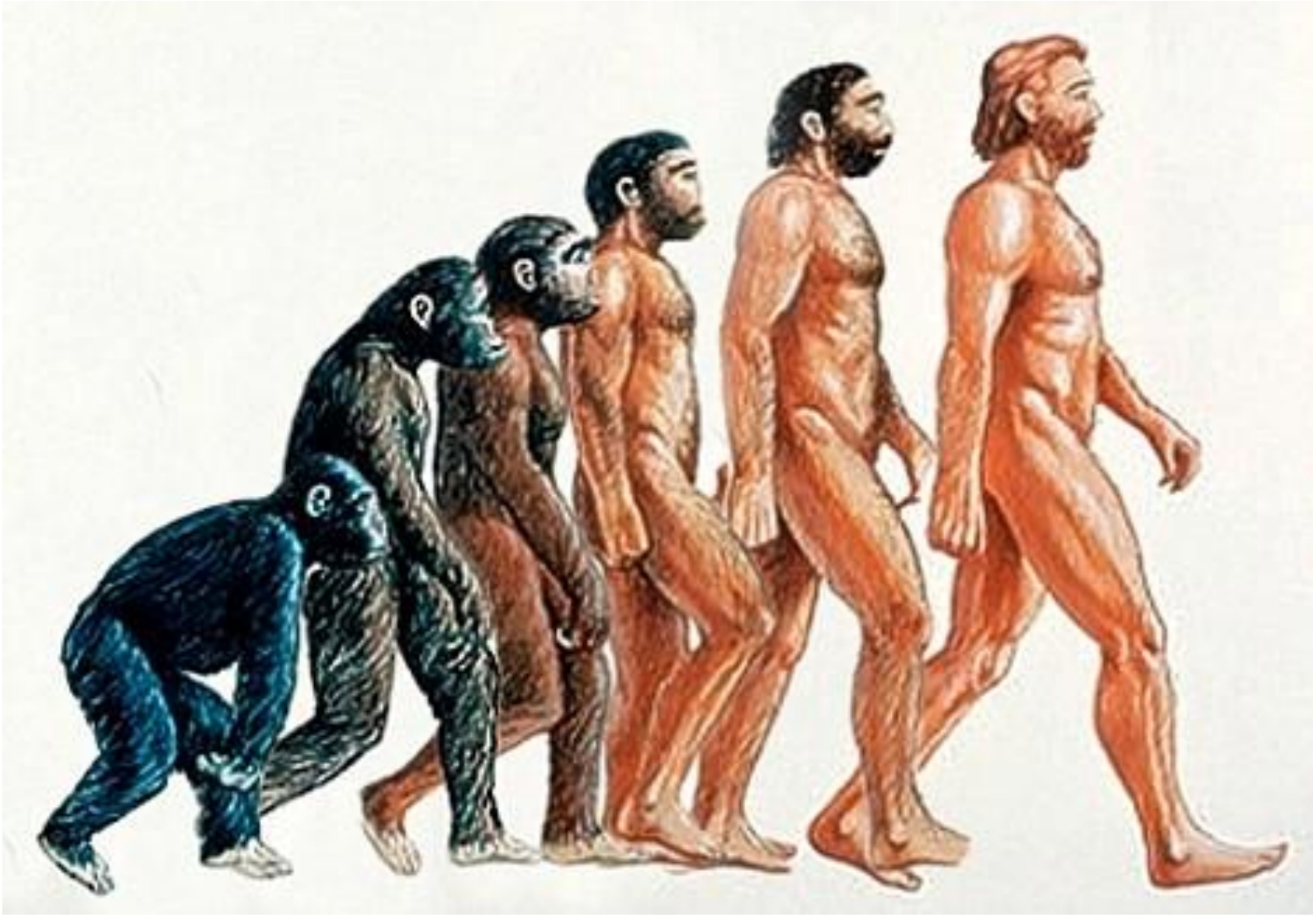
# Human Positive Selection



# Europeans

Lactase

a mutation in a regulatory region near the gene for lactase (LCT) that allows lactose tolerance to persist into adulthood. This particular variant was apparently selected in parts of Europe after the domestication of cattle.

# Frequency of the C/T-13910 allele in Lactase

The *LCT* region appears to have undergone a selective sweep 2000–20,000 years ago (4), coinciding with the domestication of cattle.

The high selection coefficient (between 0.014 and 0.15) distinguishes *LCT* as one of the most strongly selected loci in the human genome.

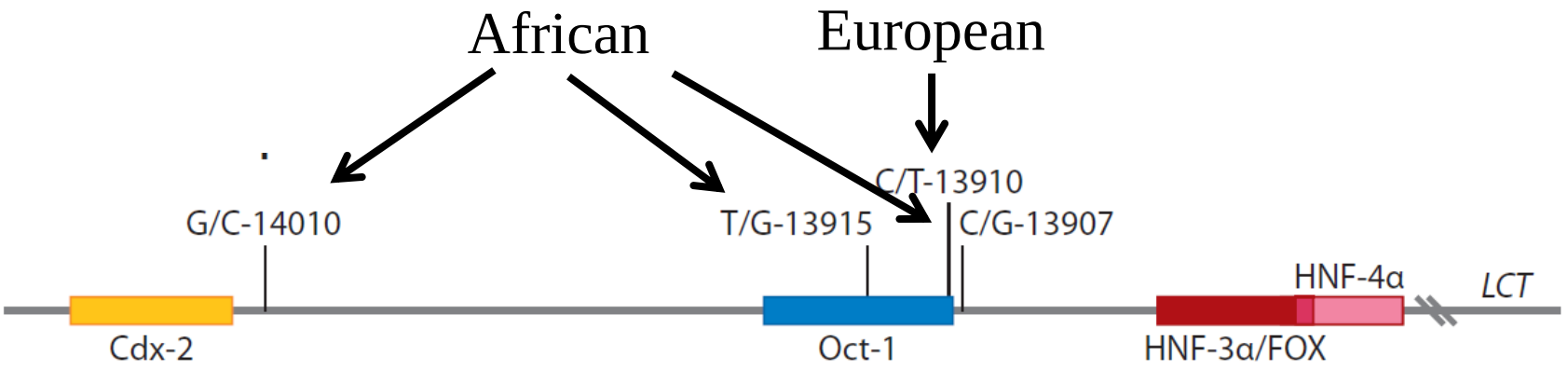
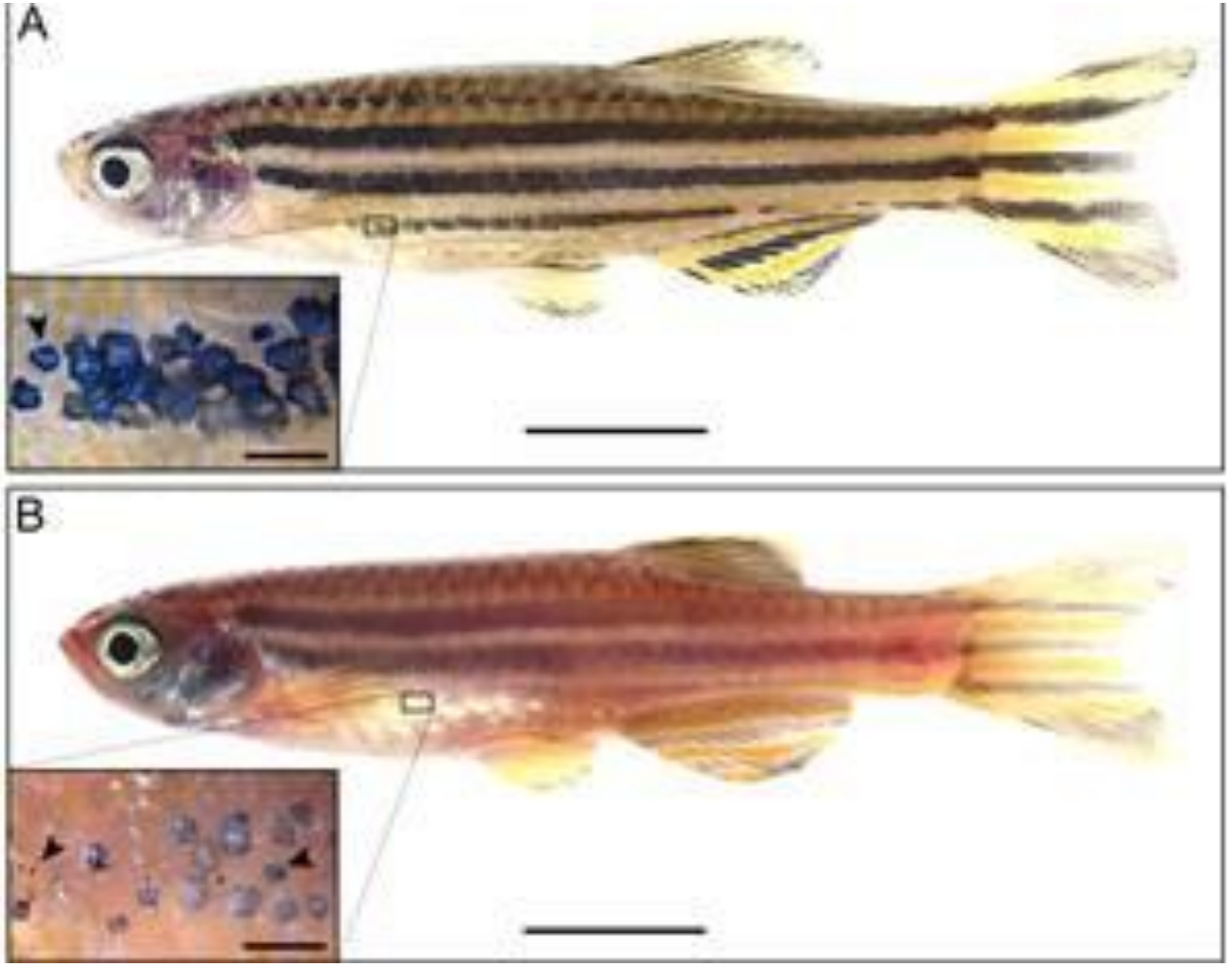
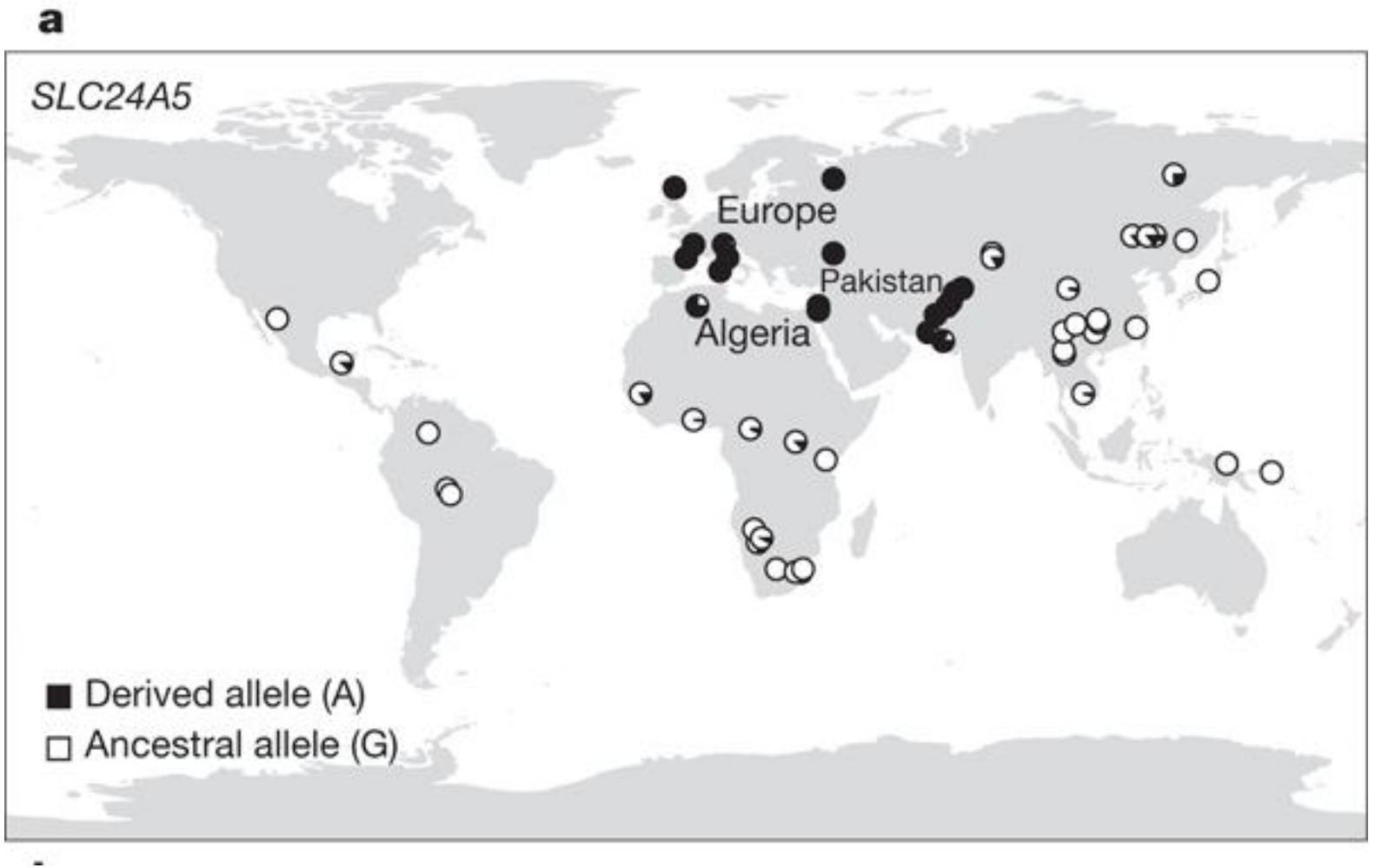



**Figure 3**

Locations of transcription factor-binding sites and predicted adaptive alleles upstream of *LCT*, the lactase gene. Three alleles were identified as potentially causal alleles in the African pastoral populations, whereas C/T-13910 was predicted to be the causal allele in Northern Europeans. Additionally, the T/G-13915 allele is correlated with lactase persistence in the Saudi Arabian population. The transcription factors and the sequence they bind in a supershift assay (48) are: HNF-4α (−13854 to −13830), HNF-3α and FOX (−13872 to −13848), Oct-1 and GAGA (−13933 to −13909), and Cdx-2 (−14040 to −14016).

# SLC24A5: skin color

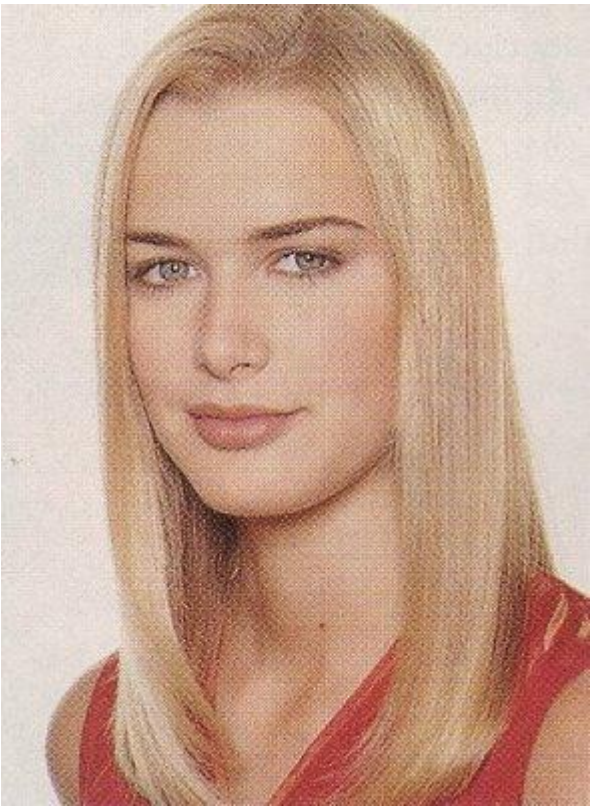




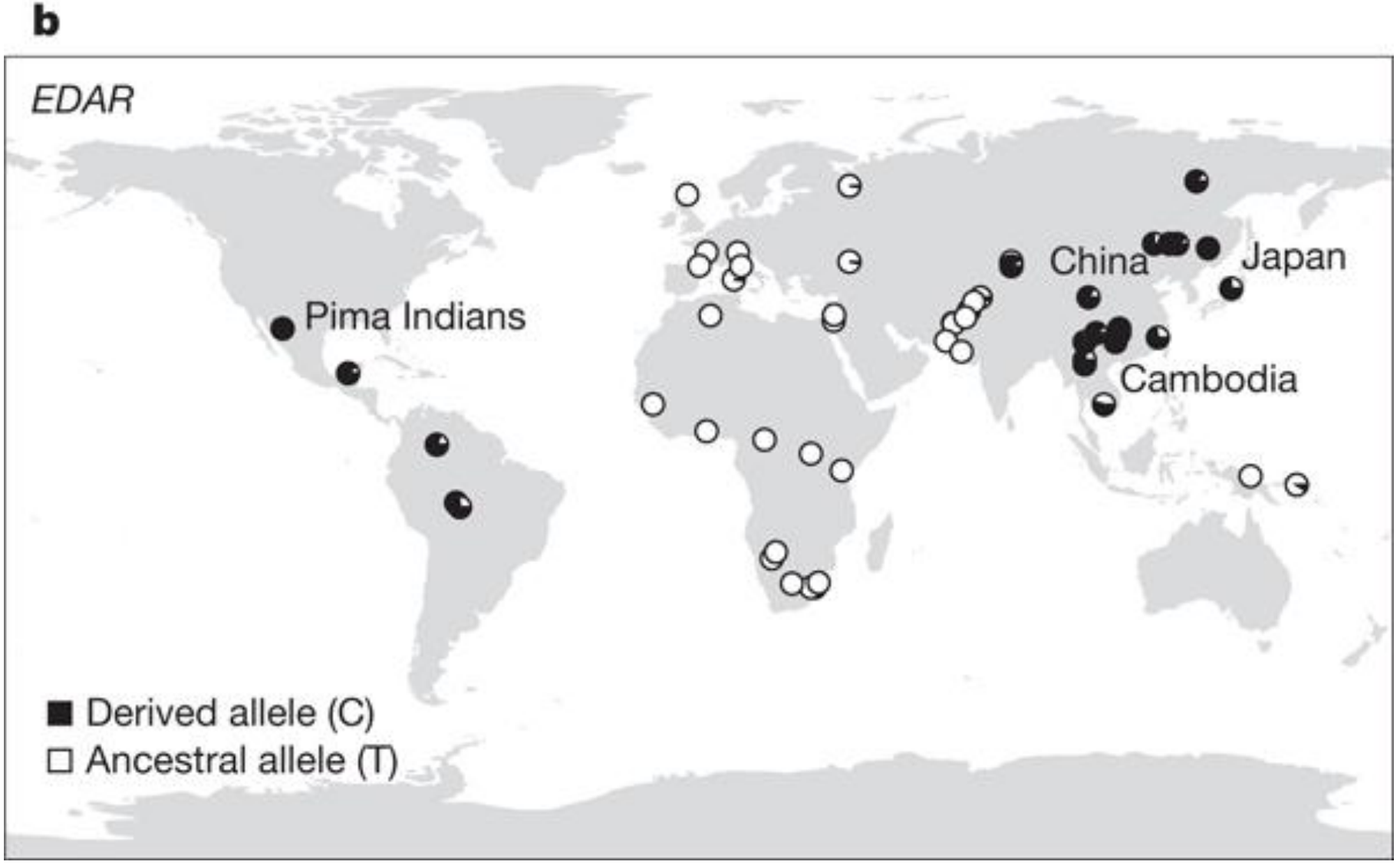

SLC24A5 involved in skin color. A111T .

SLC45A2: Also, an L374F substitution is at 100% frequency in the European sample, but absent in the Asian and African samples.

# EDAR:  Hair thickness



# Asian


b
EDAR
Pima Indians
China
Japan
Cambodia
Derived allele (C)
Ancestral allele (T)

# Asian

*EDAR* and EDA2R

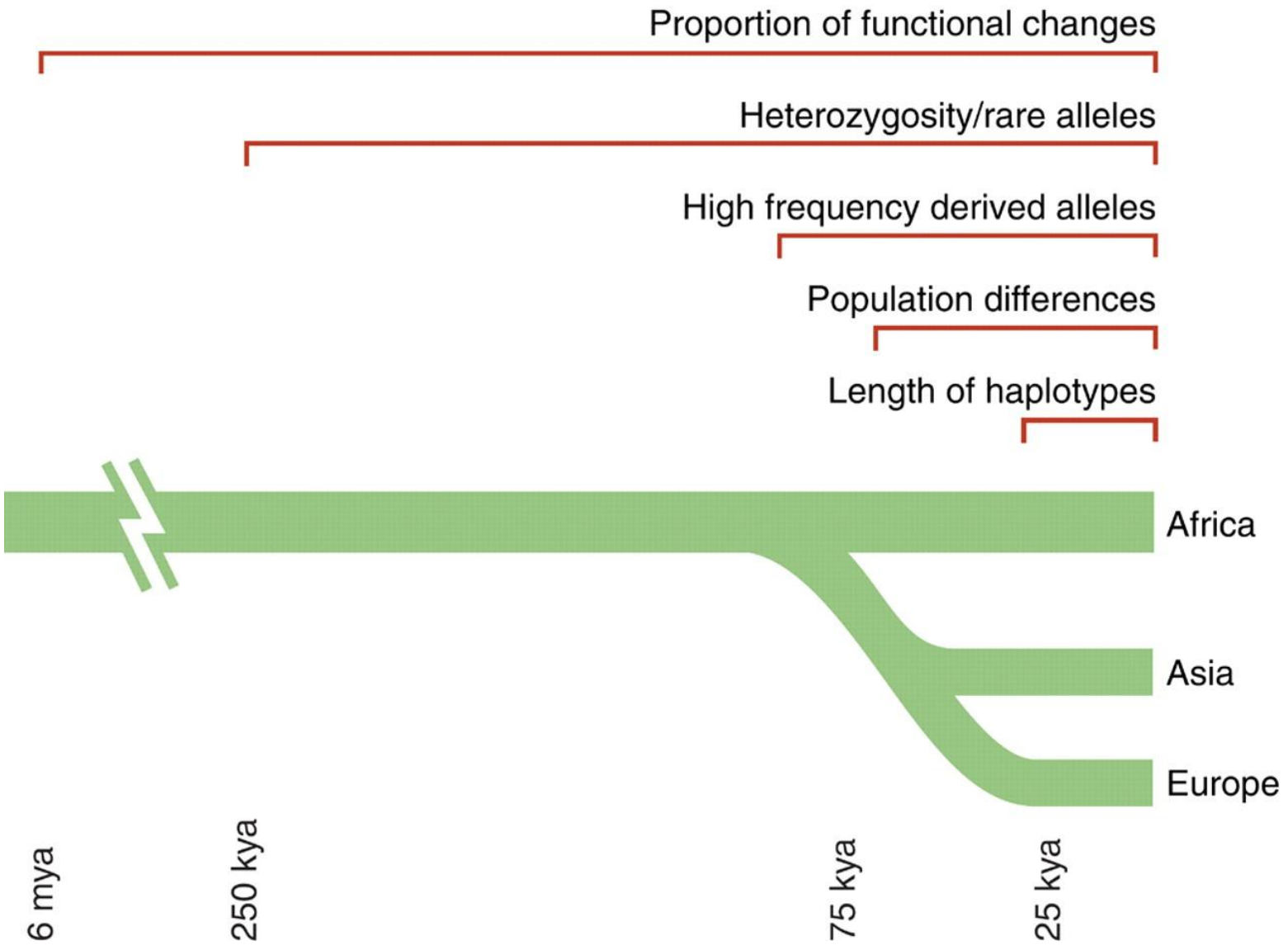
Hair morphology

have a central role in generation of the primary hair follicle

A mutation encoding a V370A substitution in *EDAR* is near fixation in Asia and absent in Europe and Africa

100% in Pima Indians and in parts of China, and 73% in Japan

**Fig. 1. Time scales for the signatures of selection.**




**P C Sabeti et al. Science 2006;312:1614-1620**

**Proportion of functional changes**

**- Positive selection may favor many alleles, not just one**

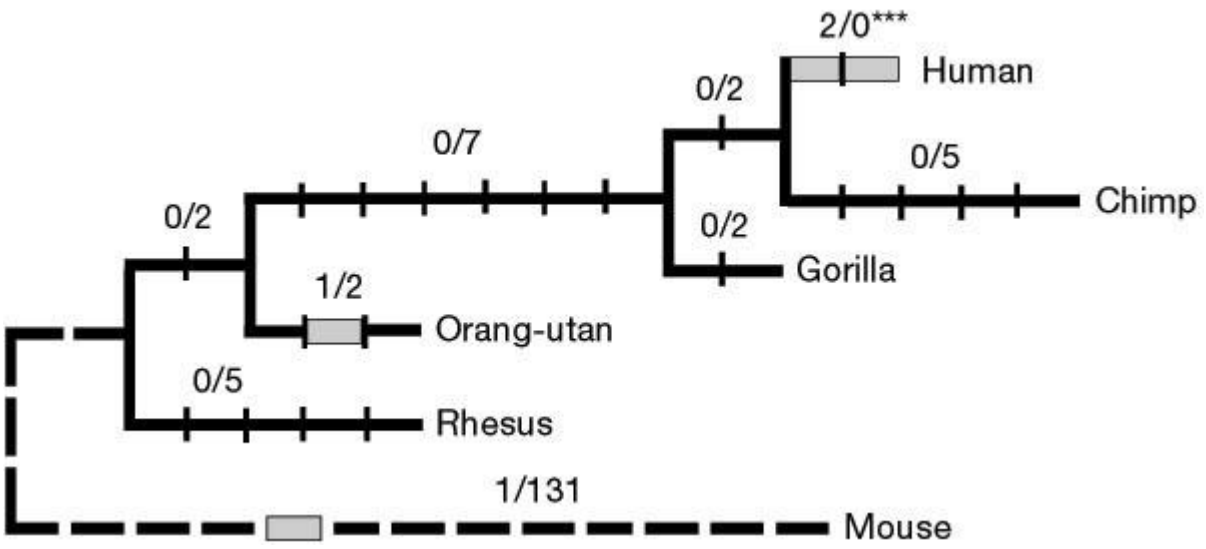
**- This can be detected by a large number of coding changes relative to neutral changes in the gene.**

# FOXP2: a transcription factor involved in human speech

Adaptively evolving along human lineage.

Highly conserved, but has recent human-specific changes

Mutations of FOXP2 cause a severe speech and language disorder




Foxp2 gene
Has high functional differences.
Bars represent nucleotide changes. Grey bars indicate amino-acid changes

Cell

Volume 137, Issue 5, 29 May 2009, Pages 961–971

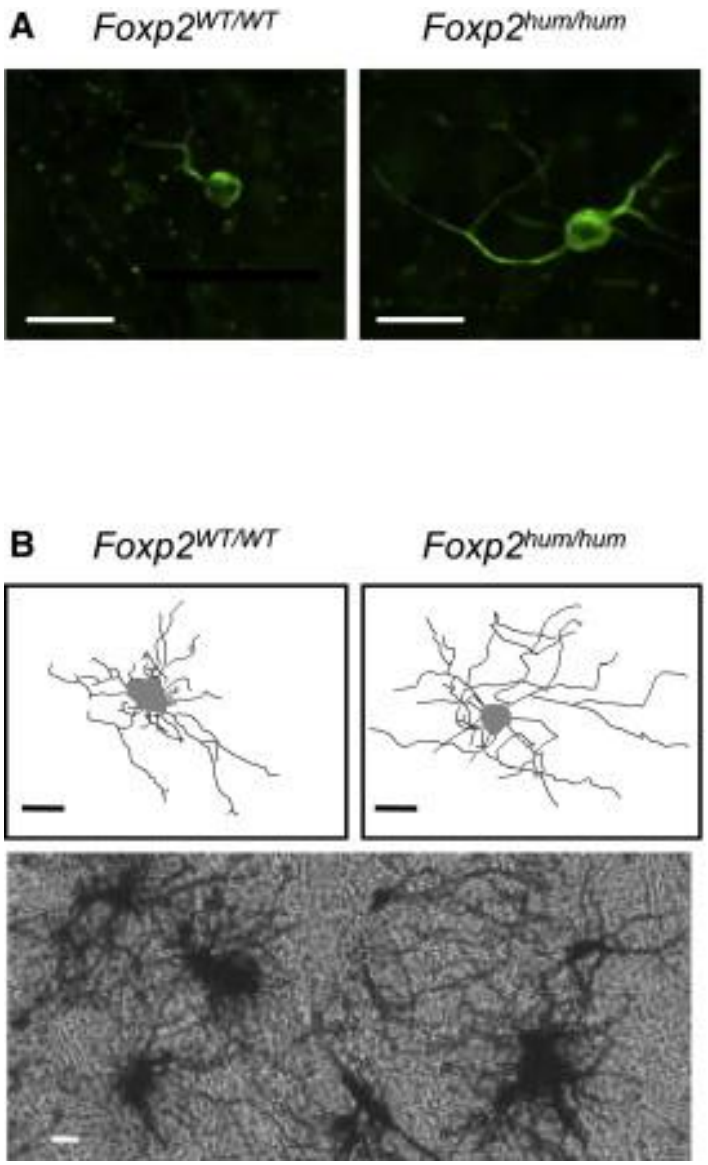
Article

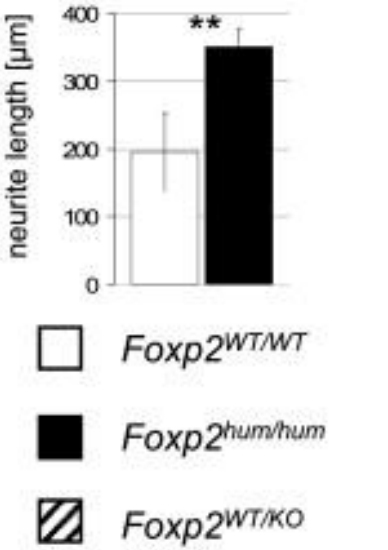
# A Humanized Version of Foxp2 Affects Cortico-Basal Ganglia Circuits in Mice

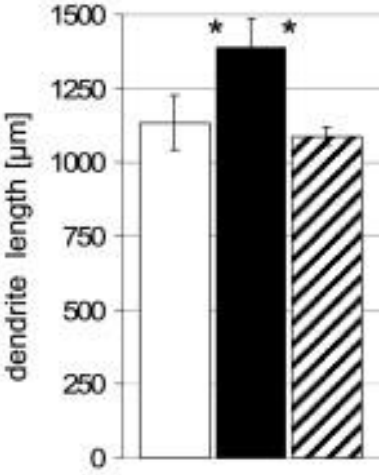
Wolfgang Enard[1], Sabine Gehre[1], Kurt Hammerschmidt[2], Sabine M. Hölter[3], Torsten Blass[1],

Replaced mouse FOXP2 with human FOXP2
Found gain-of-function changes in brain and behavior

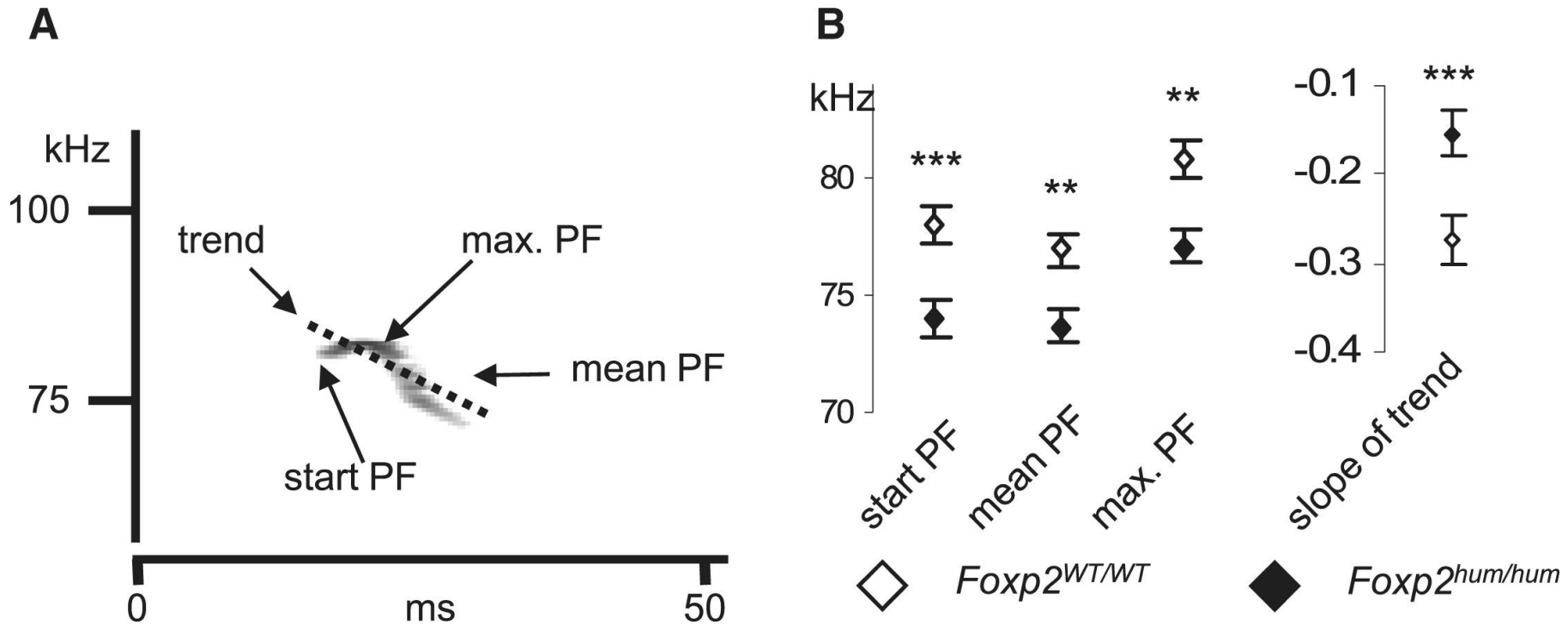
# *Foxp2*$^{hum}$ Increases the Length of Dendritic Trees



# *Foxp2*$^{hum}$ Affects the Structure of Pup Isolation Calls



**Lower Genetic Diversity**
**Heterozygosity (lower)/rare alleles (higher)**

**Selective sweep reduces genetic diversity at linked alleles.**

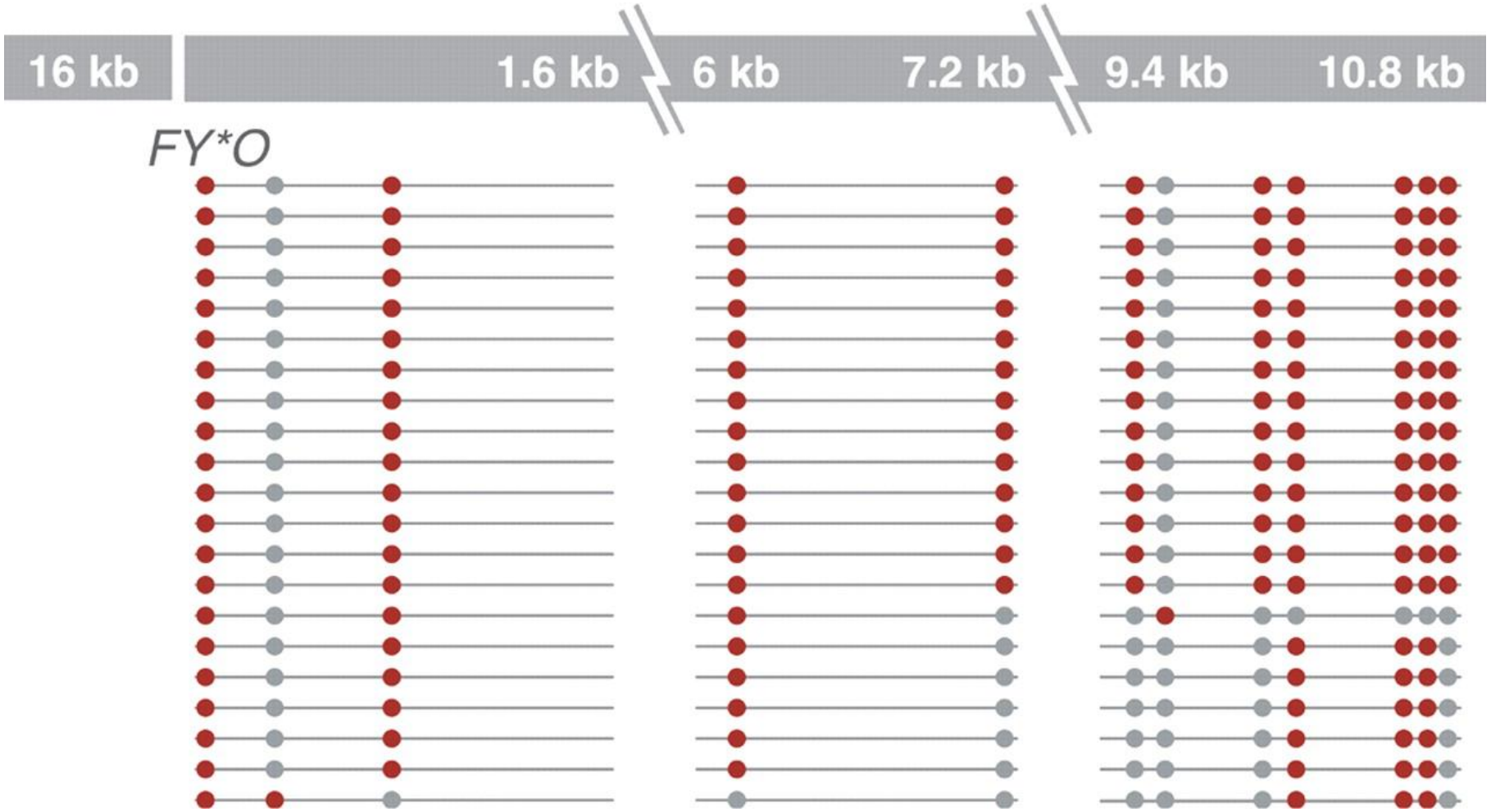
**If rare alleles are linked to the selected mutation, they increase in frequency by hitchhiking. So their frequency rises.**

**High Frequency Derived Alleles**

**Most new alleles are at low frequency**

**One way for a derived allele to become high frequency is to by linked to an allele undergoing positive selection**

**Excess of high-frequency derived alleles at the Duffy red cell antigen (FY) gene**
**Resistance to malaria.**




Red – derived. Gray – ancestral (Chimp)

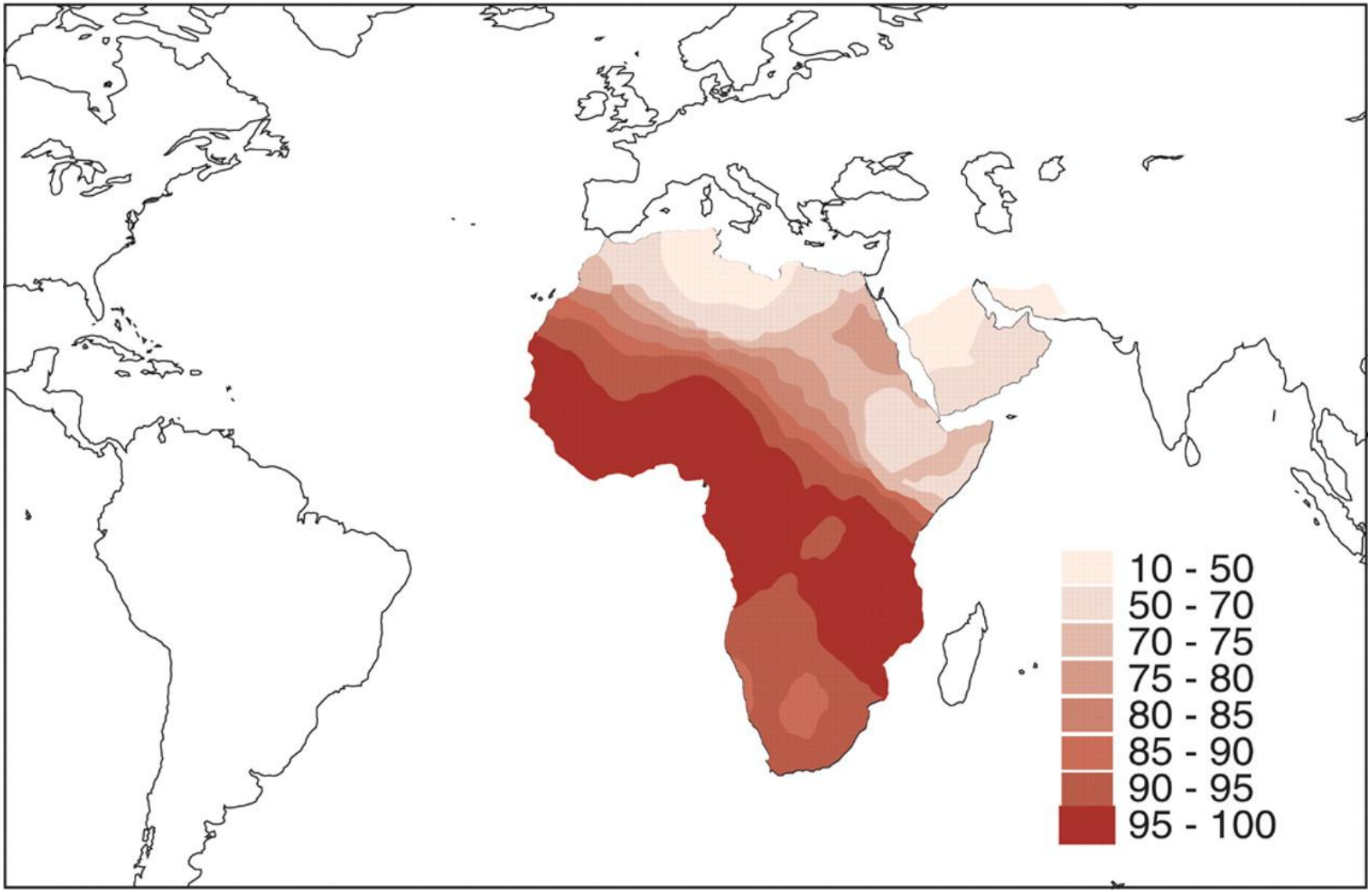
**P C Sabeti et al. Science 2006;312:1614-1620**

**Differences between populations**

**Different populations may have different selective pressures (domestication of cattle, resistance to malaria etc.)**

**Different alleles may be selected in different populations.**

## Extreme population differences in FY*O allele frequency.

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# Long Haplotype

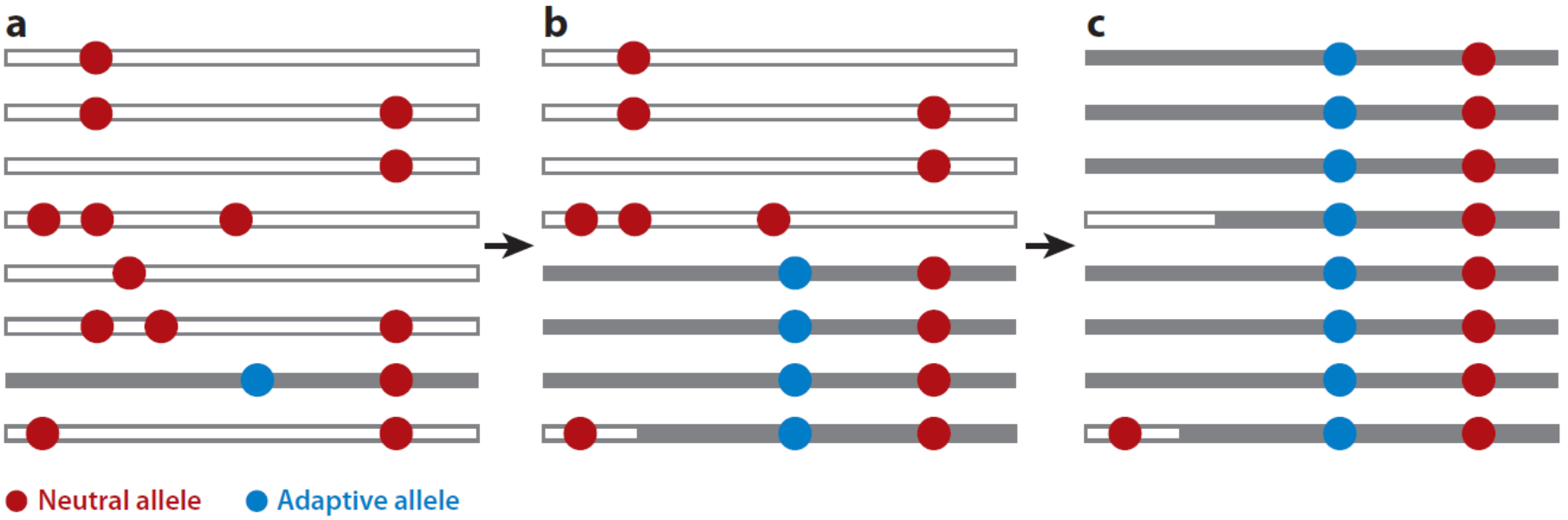
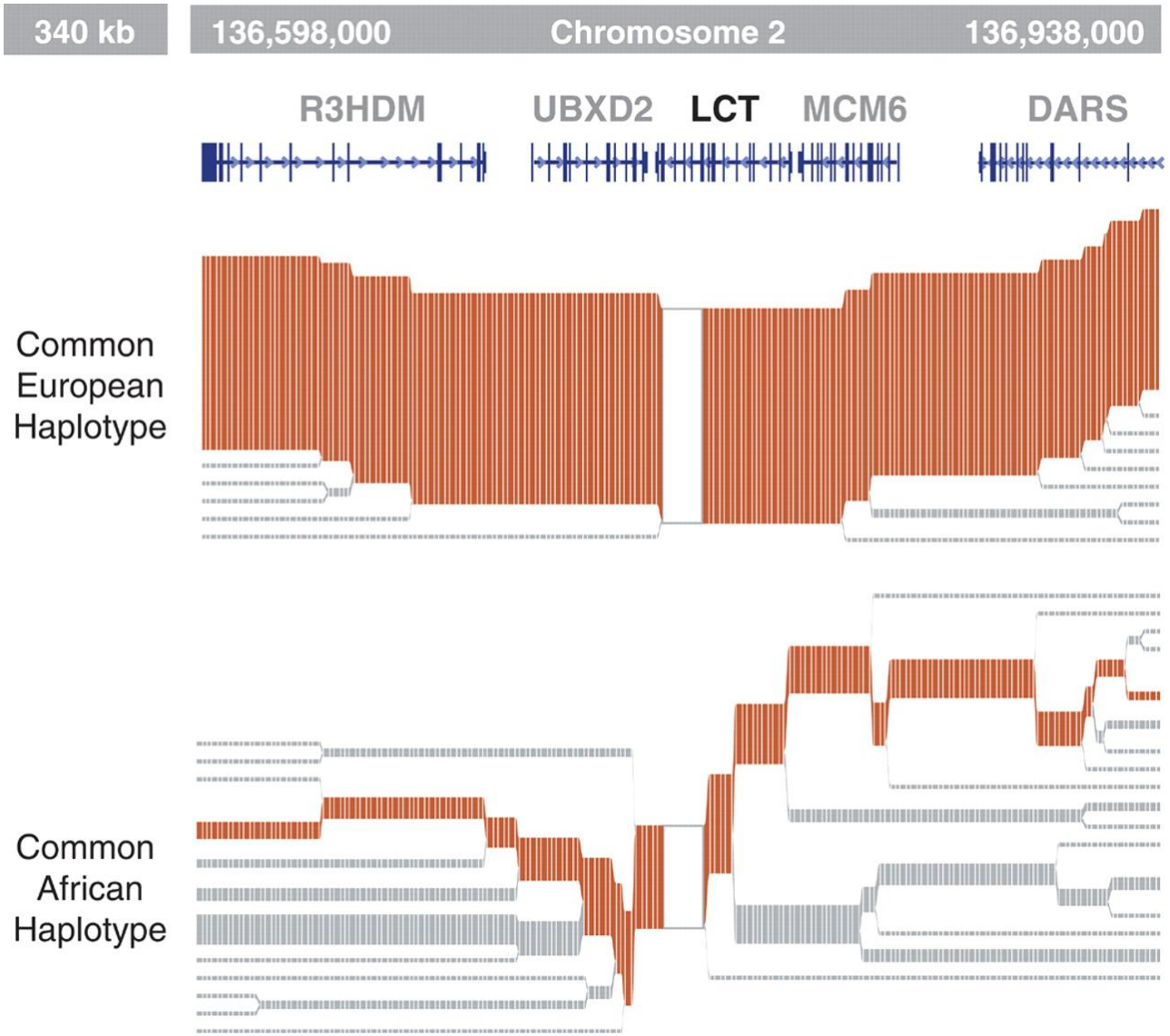



Figure 1

# Long haplotype surrounding the lactase persistence allele.

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# African American

Hemoglobin-B

Duffy antigen (FY)

- target of selection for malaria resistance

LARGE

*DMD*

- resistance to Lassa fever.