

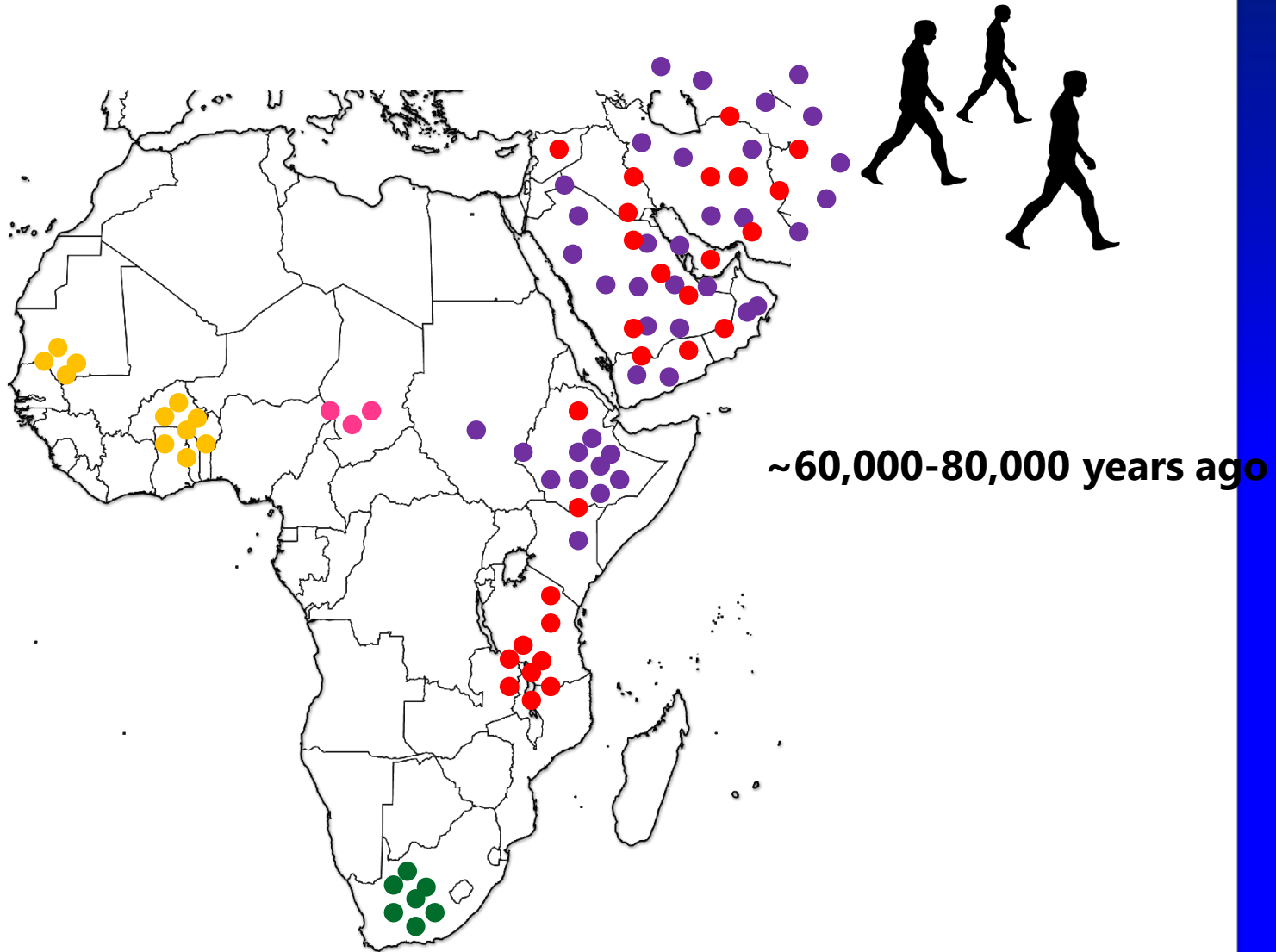
The evolution of complex traits in diverse human populations



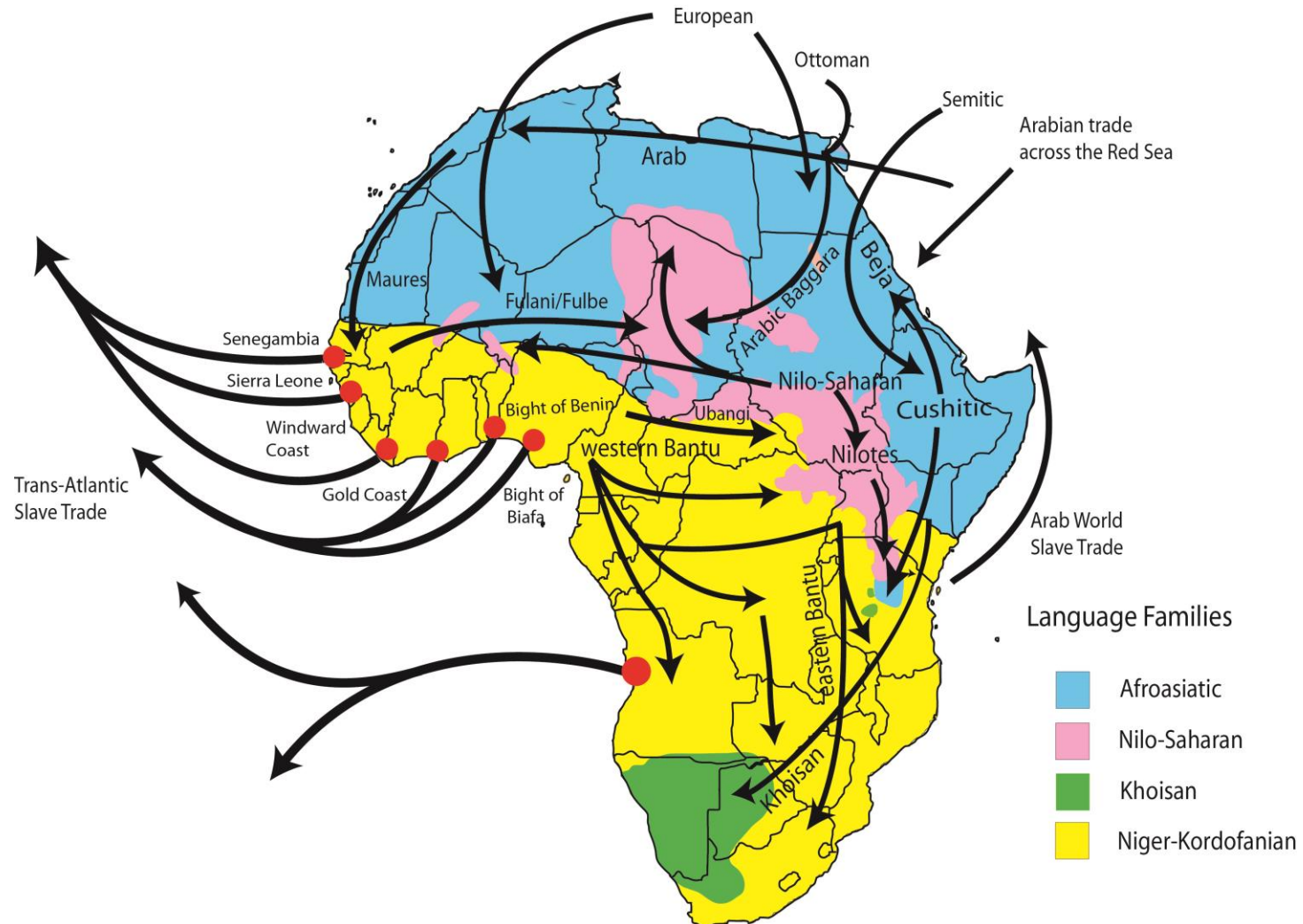
General Outline

- I. Introduction to Patterns of Human Diversity and Evolution**
- II. Case Study of Natural Selection in Action: Lactase Persistence**
- III. The relationship between evolutionary history and complex disease susceptibility in human populations.**

Recent African Origin model of human evolution



Past migration events in Africa



(Campbell et al., *Current Opinion in Genetics & Development*, 2014)

Genes, phenotypes, and natural selection

Natural selection and selective pressures
(eg. environment and culture)



Traits/Phenotypes



Genetic variation underlying traits/phenotypes
under selection

Genetic Origins of Lactase Persistence and the Spread of Pastoralism in Africa

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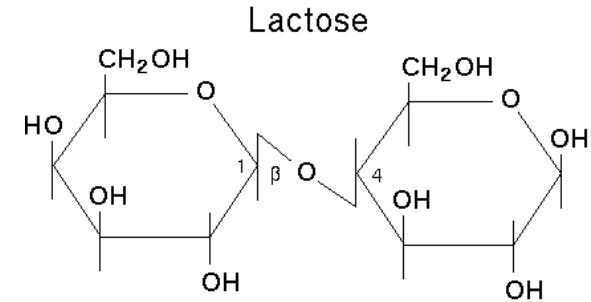
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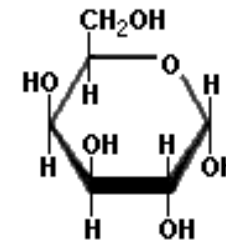


What is Lactose?

- It is a sugar present in milk. The amount varies among species. The principal function is to provide energy for the newborn.



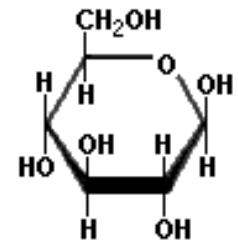
Lactase



Galactose



Bloodstream



Glucose

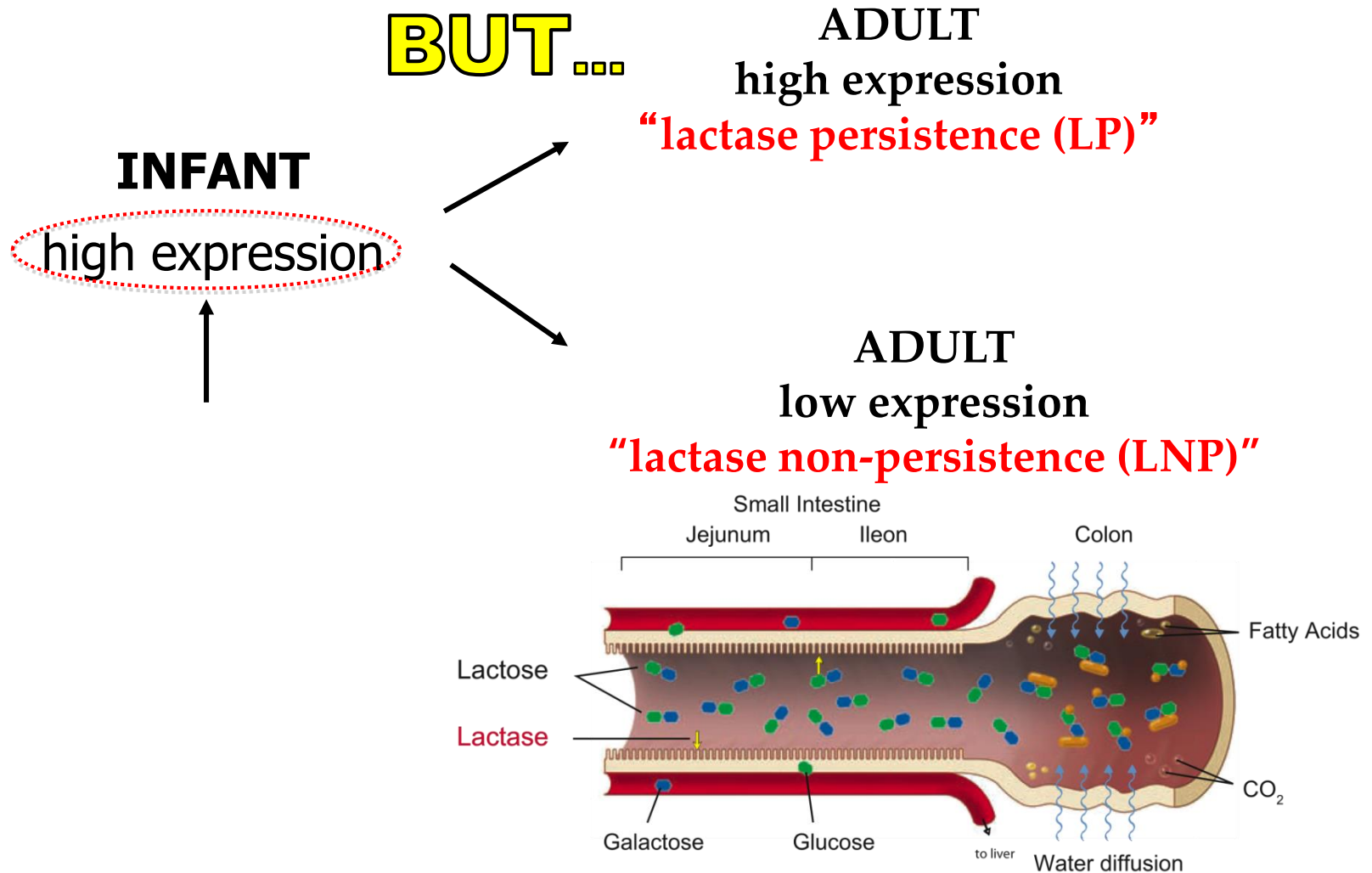


Bloodstream

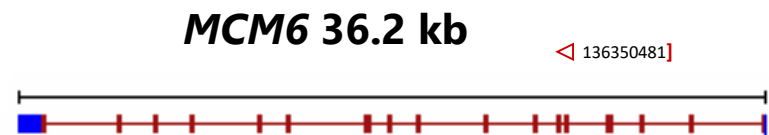
What is Lactase?

- It is an enzyme expressed in the small intestine that digests lactose into two simple sugars which can be easily absorbed into the bloodstream.

- After weaning, the activity level of the lactase enzyme decreases and the ability to digest lactose also declines.



Genetics of LP in European populations



Intron 13 (3.2 kb)

...GTCCC**C/T**GATGTAATAGAA

T-13910

SNPs associated
100% with LP in
Finns

Intron 9 (1.3 kb)

...GGTGGC**G/A**CGG...

A-22018

Prior pivotal study on LP trait in East Africa

ARTICLES

nature
genetics

Convergent adaptation of human lactase persistence in Africa and Europe

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A SNP in the gene encoding lactase (*LCT*) (C/T-13910) is associated with the ability to digest milk as adults (lactase persistence) in Europeans, but the genetic basis of lactase persistence in Africans was previously unknown. We conducted a genotype-phenotype association study in 470 Tanzanians, Kenyans and Sudanese and identified three SNPs (G/C-14010, T/G-13915 and C/G-13907) that are associated with lactase persistence and that have derived alleles that significantly enhance transcription from the *LCT* promoter *in vitro*. These SNPs originated on different haplotype backgrounds from the European C/T-13910 SNP and from each other. Genotyping across a 3-Mb region demonstrated haplotype homozygosity extending >2.0 Mb on chromosomes carrying C-14010, consistent with a selective sweep over the past ~7,000 years. These data provide a marked example of convergent evolution due to strong selective pressure resulting from shared cultural traits—animal domestication and adult milk consumption.

In most humans, the ability to digest lactose, the main carbohydrate present in milk, declines rapidly after weaning because of decreasing levels of the enzyme lactase-phlorizin hydrolase (LPH). LPH is predominantly expressed in the small intestine, where it hydrolyzes

lactase persistence trait: C/T-13910 and G/A-22018, located ~14 kb and ~22 kb upstream of *LCT*, respectively, within introns 9 and 13 of the adjacent minichromosome maintenance 6 (*MCM6*) gene⁴ (Fig. 1). The T-13910 and A-22018 alleles were 100% and 97% associated with

Lactase persistence (LP) in Africa

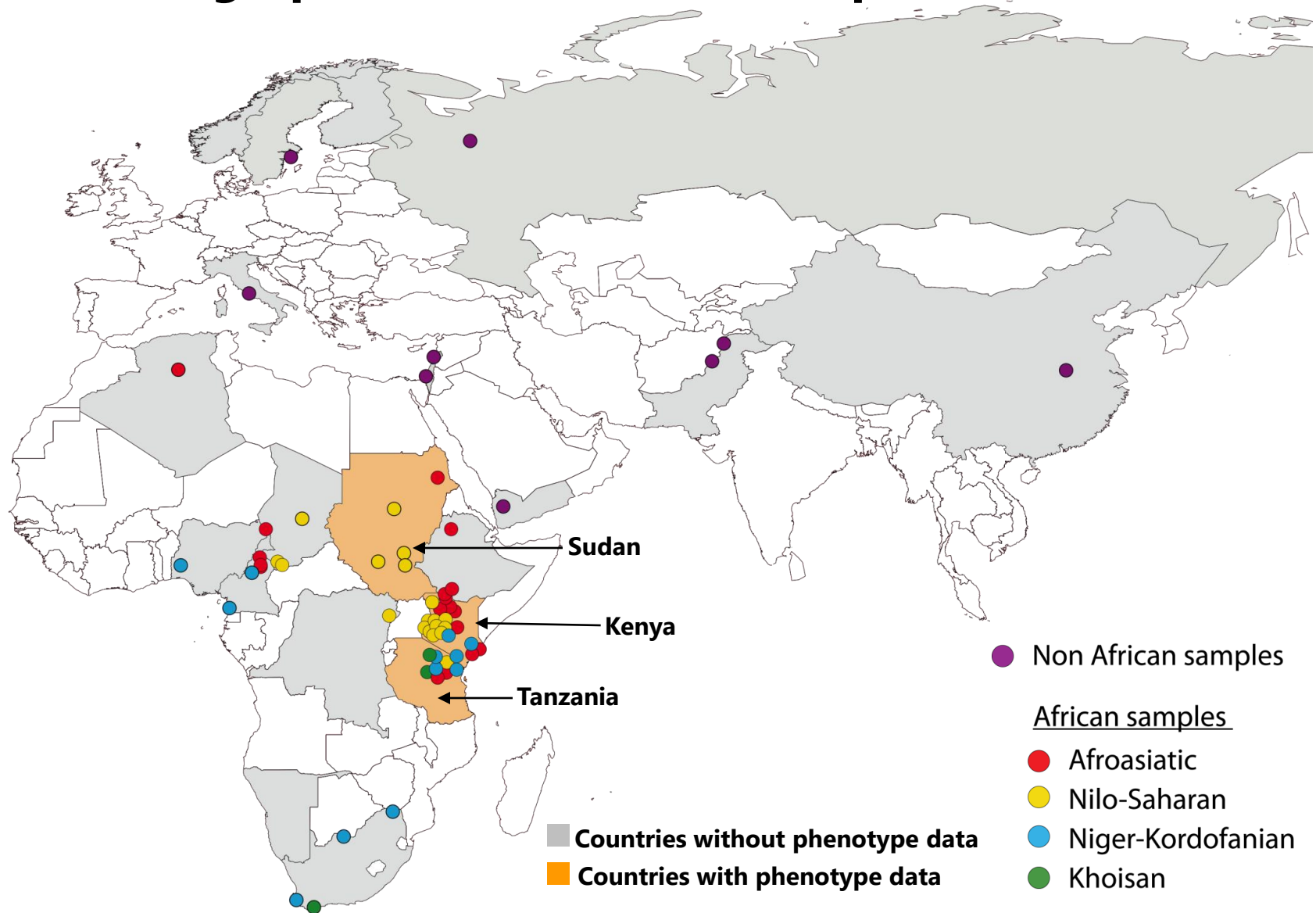
- To further understand the genetic basis of LP in African populations, intron 13 and intron 9 of *MCM6* and the *LCT* gene promoter region were sequenced:

Specific questions:

- Are there additional variants in these regulatory regions associated with LP?
- Are there signatures of selection at these associated variants?

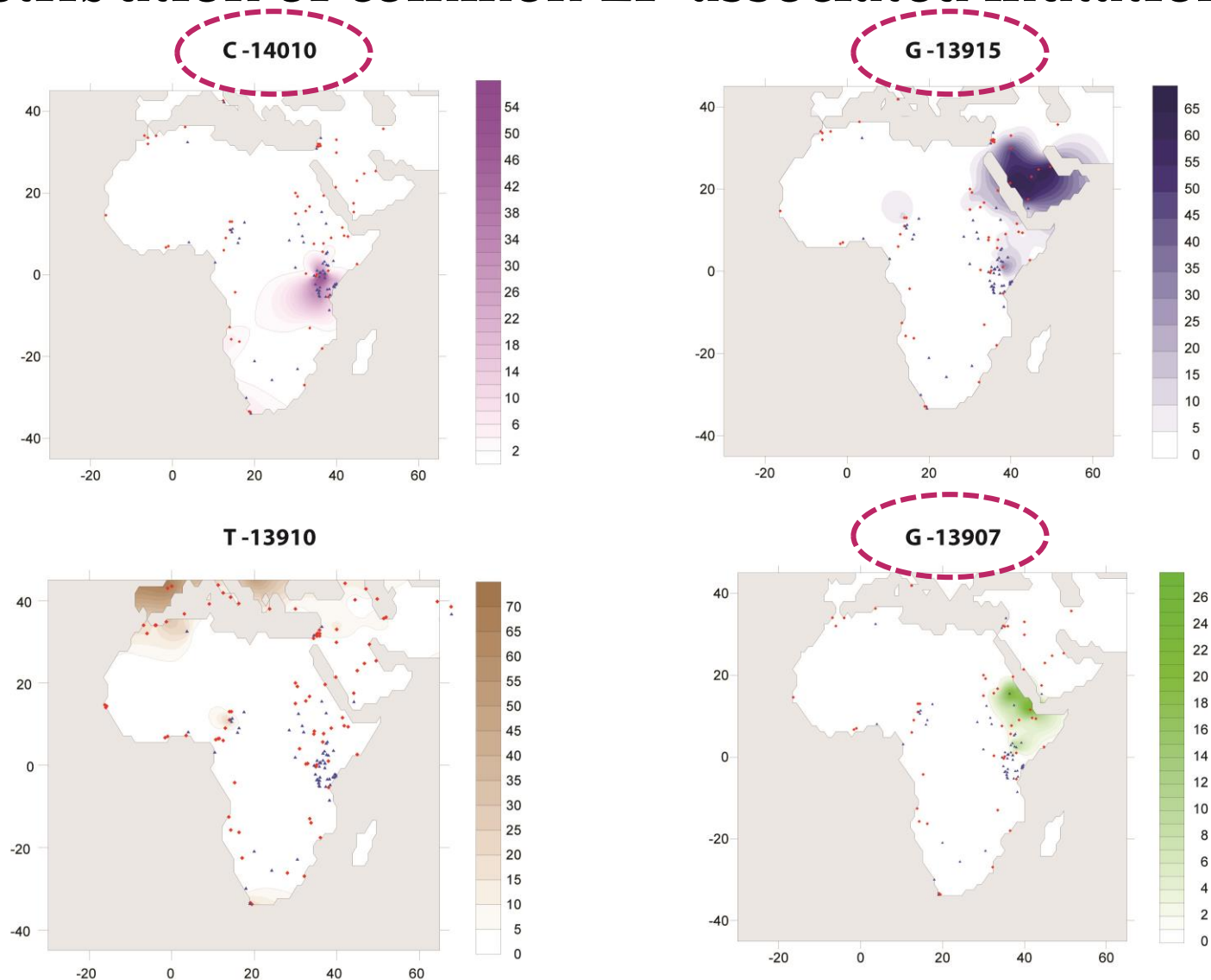


Geographic distribution of samples (N=973)



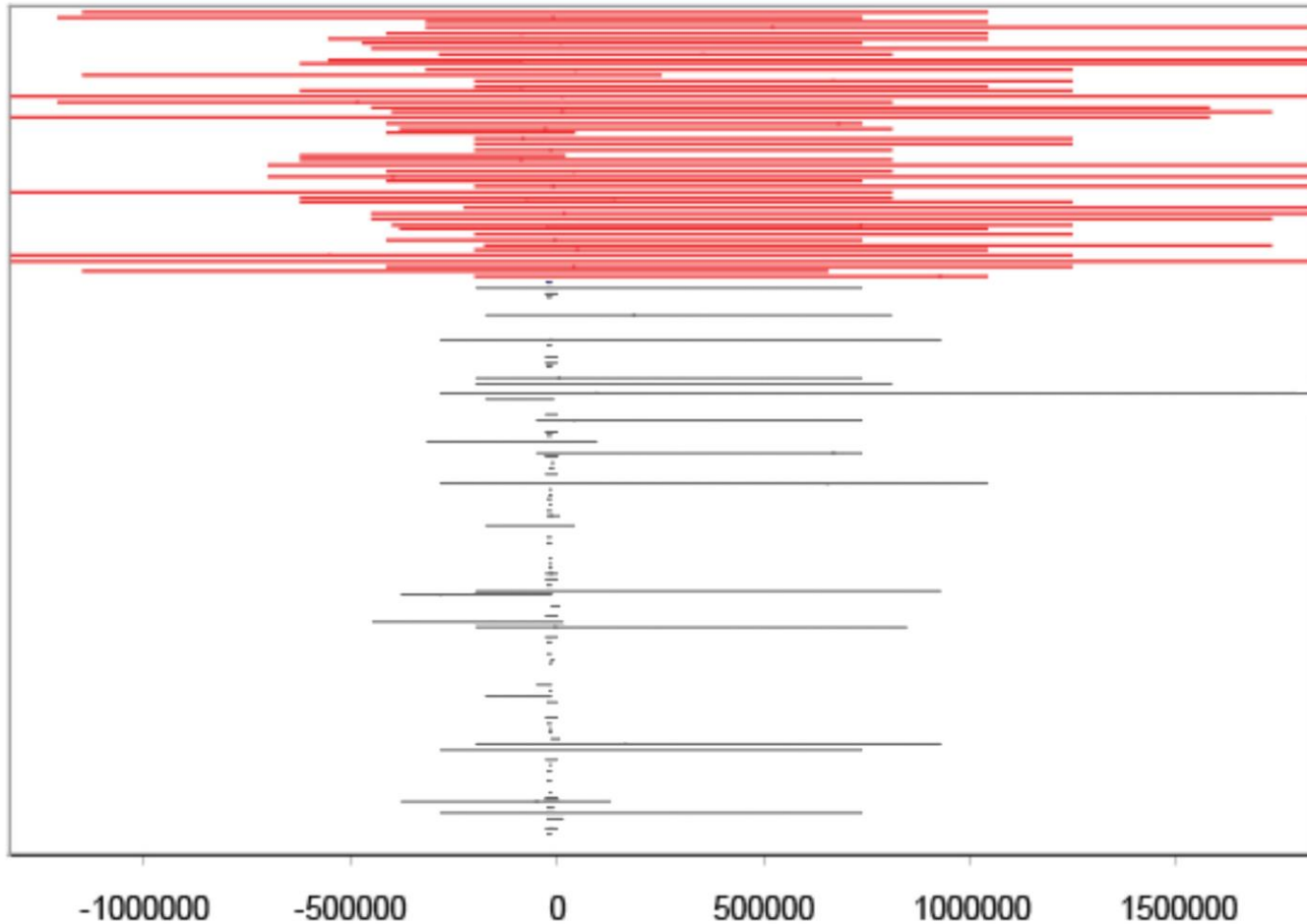


Distribution of common LP-associated mutations



(A. Ranciaro, M.C. Campbell et al., *AJHG*, 2014)

Long range of haplotypes for C-14010



(A. Ranciaro, M.C. Campbell et al., *AJHG*, 2014)

Summary

- We confirmed the presence of the three LP-associated variants in eastern African pastoralist populations.
- The distribution of some of these variants was shown to be regionally-specific (private) in Africa.
- We detected strong signatures of selection for LP-associated SNPs based on iHS mainly in pastoralist populations.
- Lactase persistence not only is an example of local adaptation in response to diet, but a striking example of convergent evolution.

Genomic Basis of Ethnic Disparities in the Onset and Progression of Uterine Serous Carcinoma in African American Women

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Modern challenges in the post-genome world

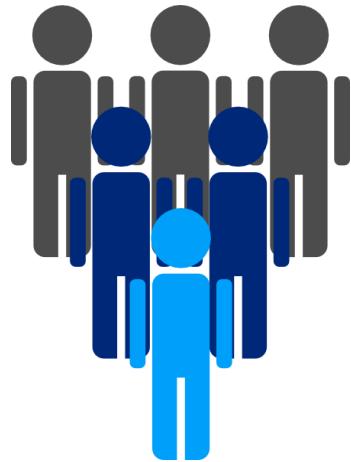
- Uterine Serous Carcinoma (USC), constitutes ~10% of all endometrial cases, and the survival rate can be as low as 50%.
- African American women have a 3-fold greater incidence of USC compared to European American women, and they tend to die early and quickly from this disease.
- One of the challenges now is to understand the genetic factors contributing to this health disparity.



Comparative analysis of USC patient genomes (preliminary cohort of N=34)

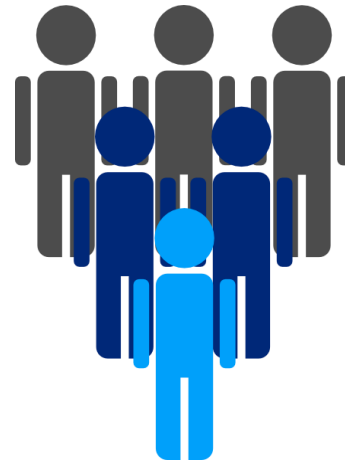
African Americans (N=13)

Avg. Age= 57.5 years



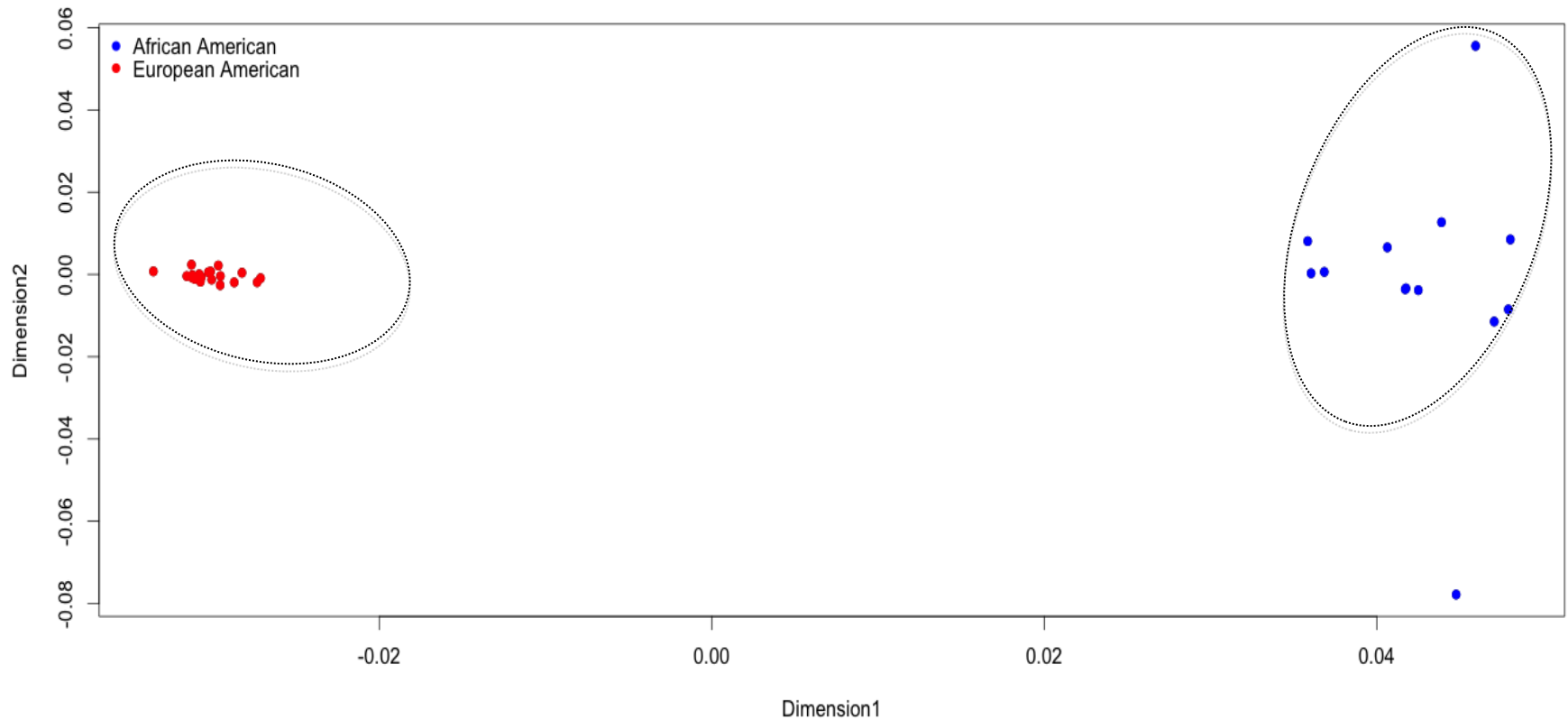
European Americans (N=21)

Avg. Age= 66.9 years



Exome data consisted of genome-wide coding sequence variation
(~500,000 SNPS)

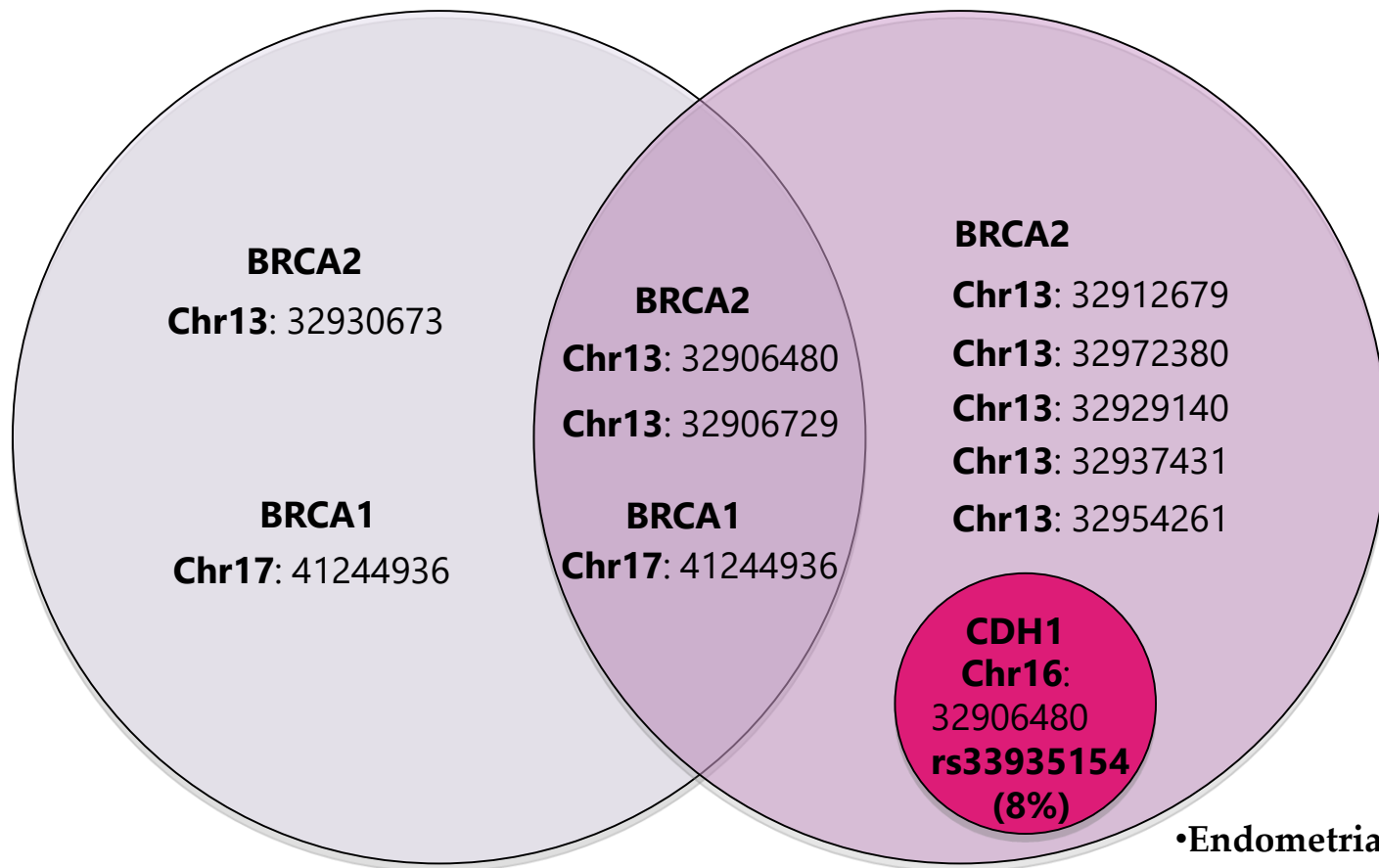
Multidimensional scaling plot for 34 USC patients



Known mutations associated with breast, ovarian and endometrial cancer (in 34 USC Patients)

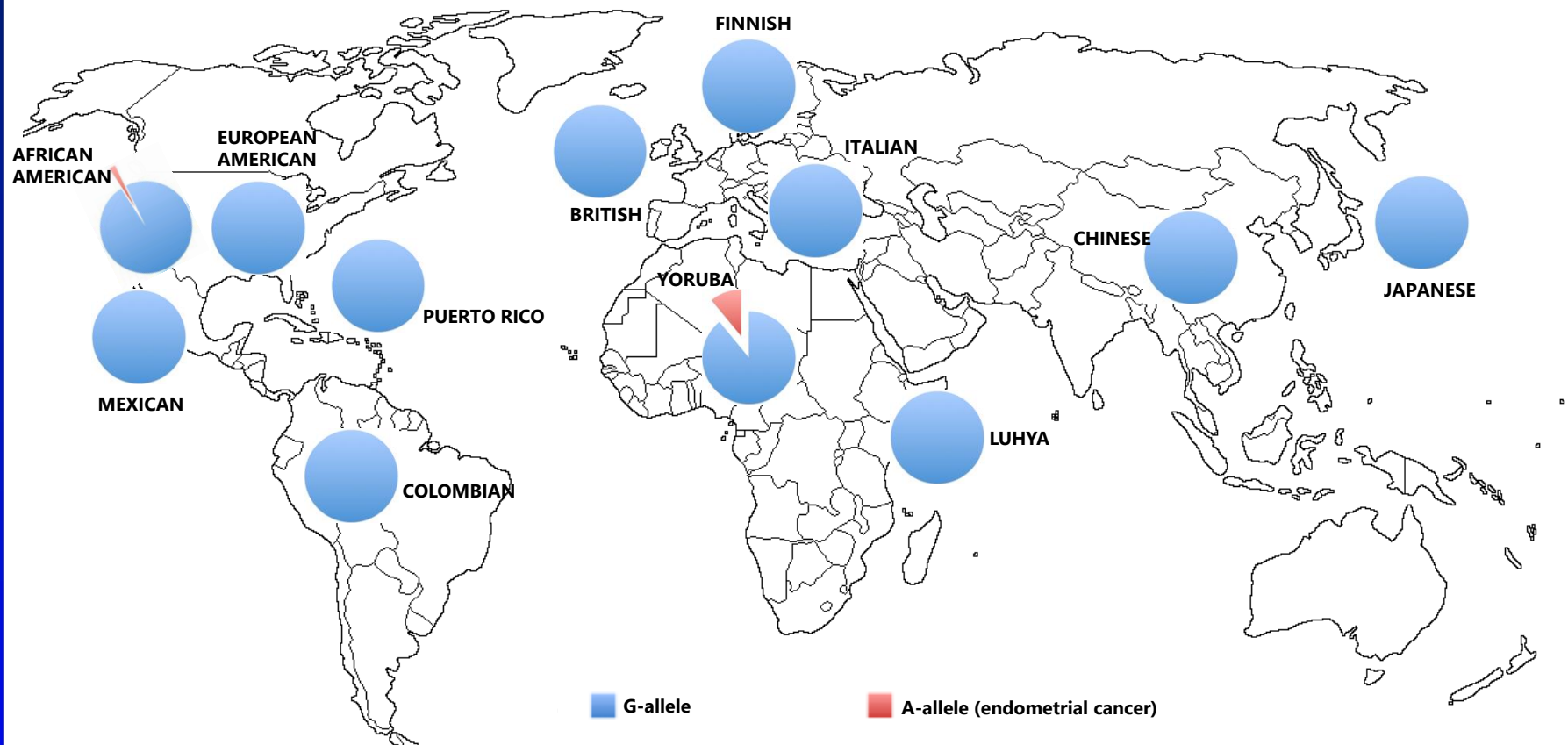
European Americans (N=21)

African Americans (N=13)



- Endometrial cancer
- Cancer Metastasis

Global distribution of allelic variation at *rs33935154* (*CDH1* gene)



CONCLUSIONS

- ❖ We identified a rare mutation (*rs33935154*) associated with endometrial cancer in an African American individual. However, this mutation was not present in our European American samples
- ❖ Globally, *rs33935154* A-allele occurs at low frequency (~10%) in populations of African descent (while it is absent in non-African populations), representing a potential ethnic-specific biomarker.
- ❖ Our preliminary data reinforce the need for interrogating regions of the genome enriched for West African ancestry to identify novel mutations that likely play a role in the differential onset and/or progression of USC.
- ❖ Some of these alleles may be private to populations due to evolutionary history.

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