

Leveraging the Genetics of
***Racially Mixed* Children to Advance**
Precision Medicine

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**American Indian
and Alaska Native**

Multiracial

**Native Hawaiian
and Other Pacific
Islander**

Asian

Latino

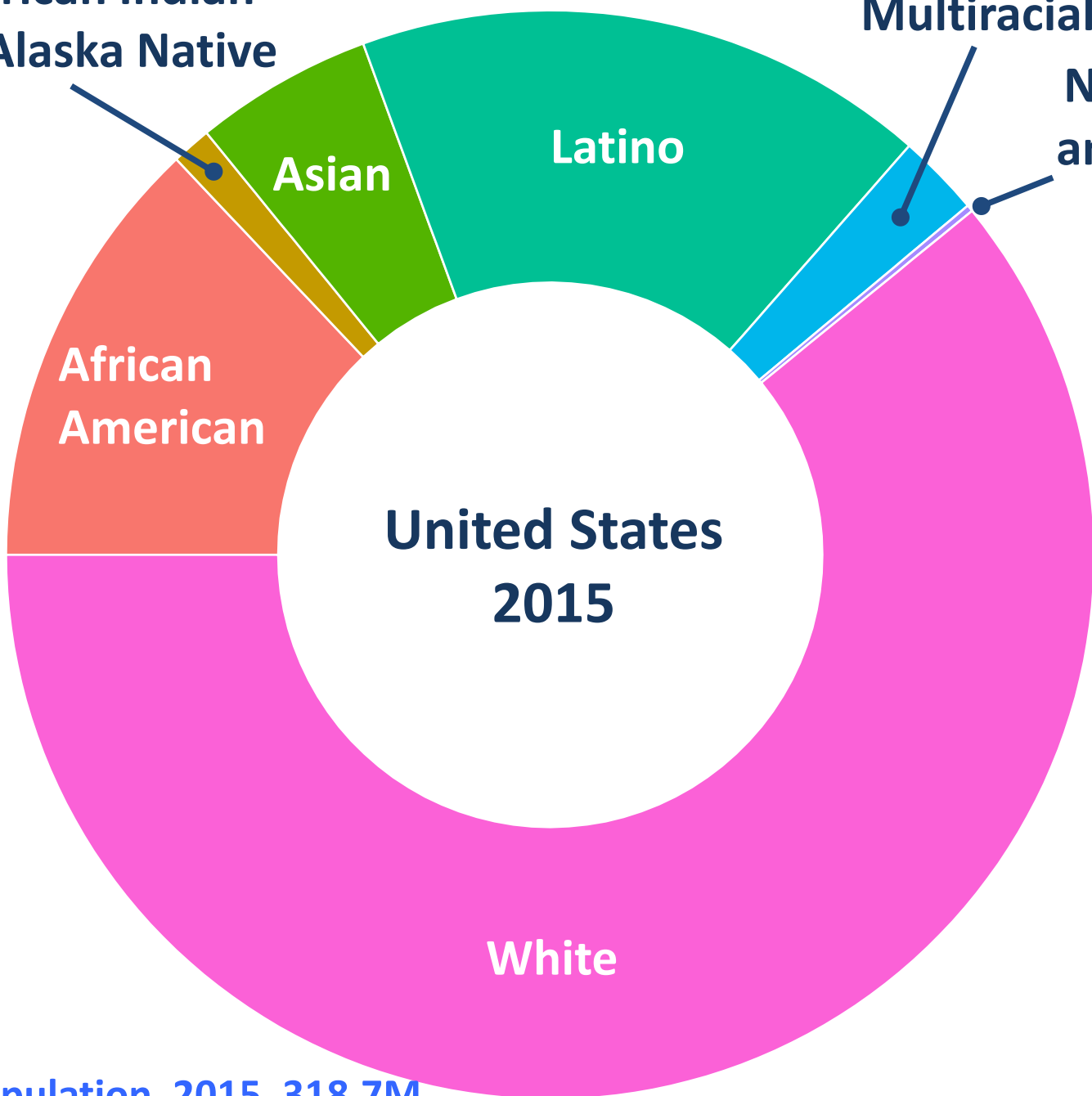
**African
American**

**United States
2015**

White

U.S. Population, 2015. 318.7M

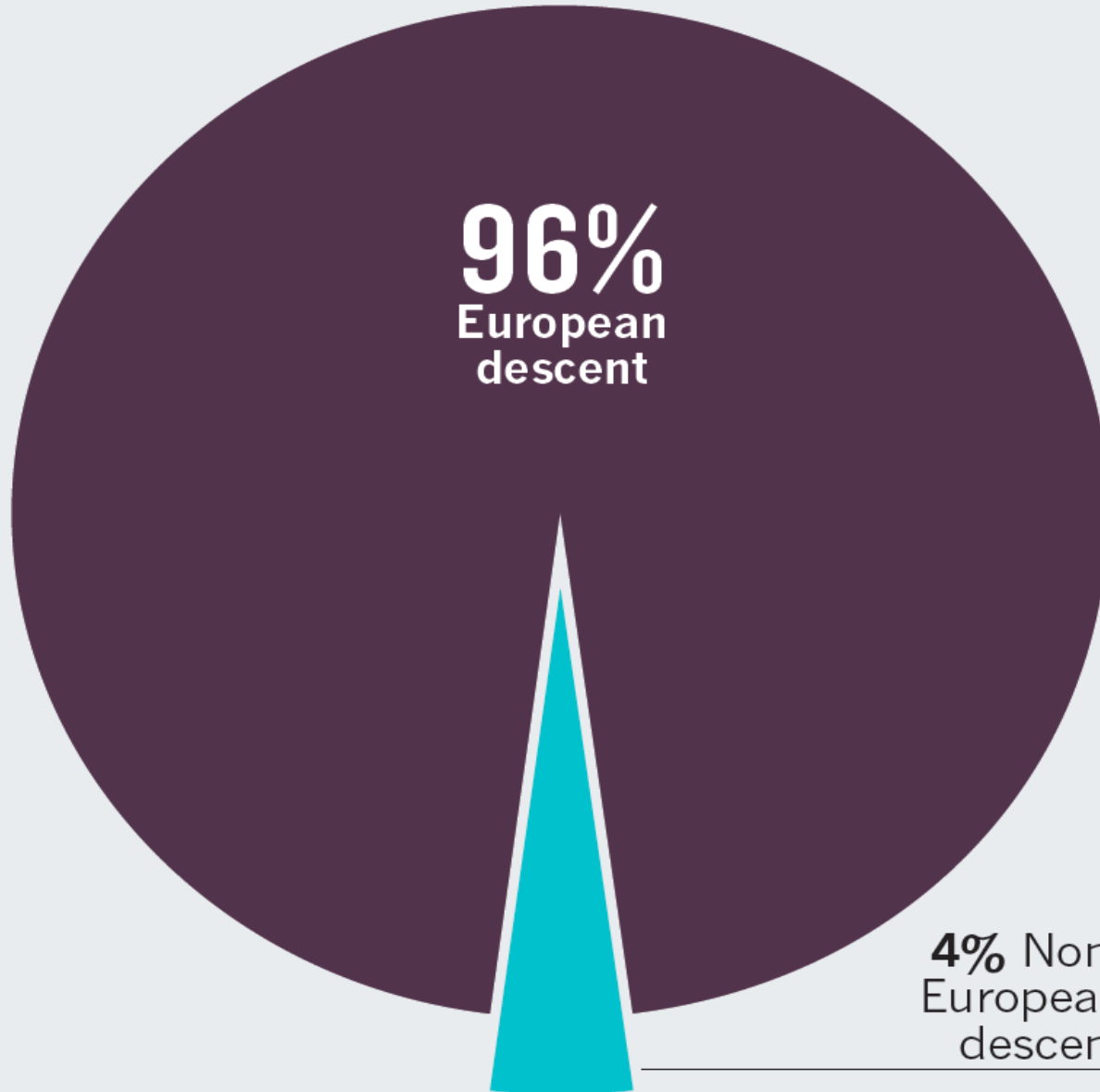
UCSF



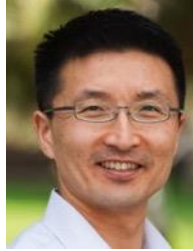


SAMPLING BIAS

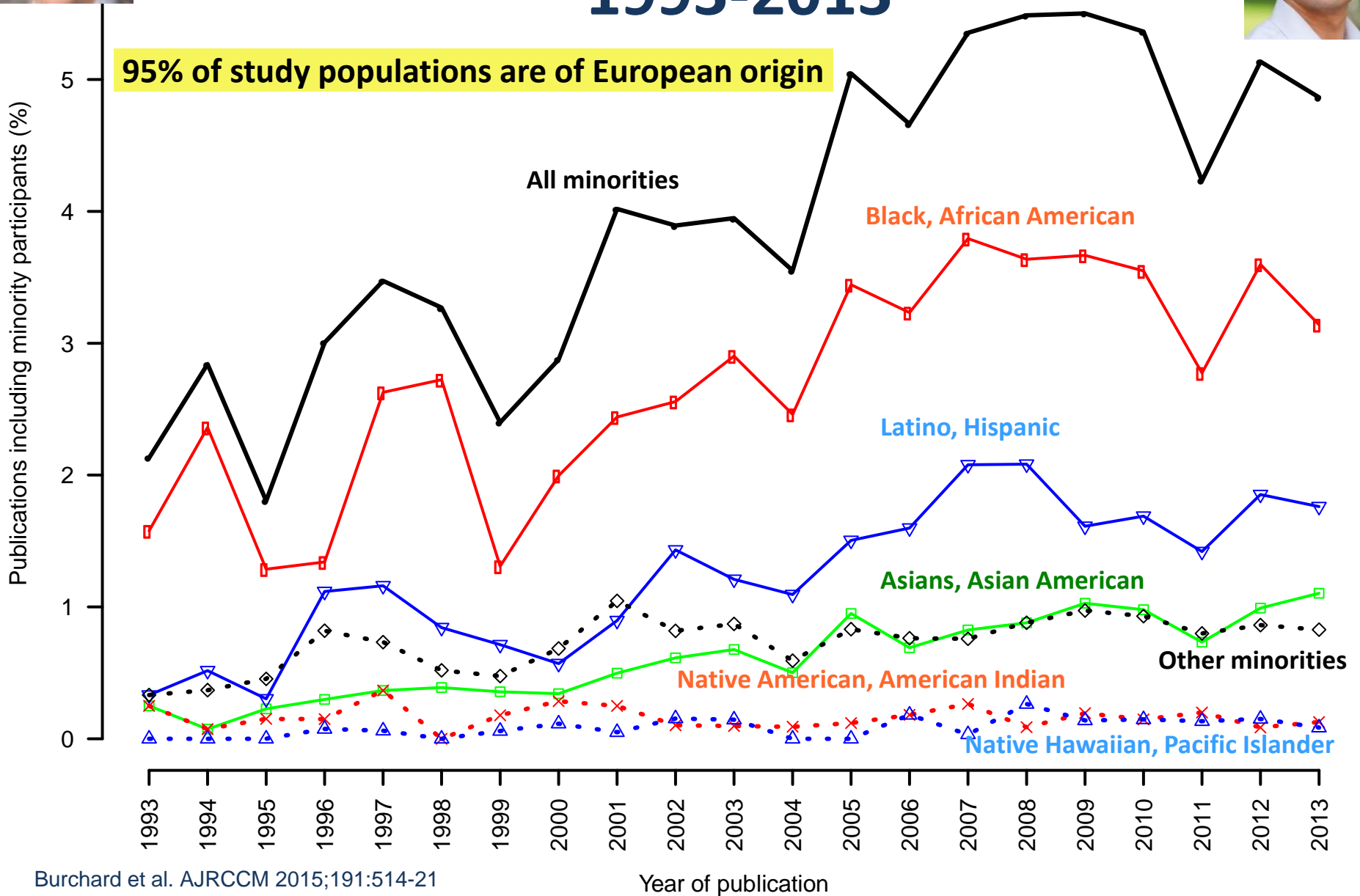
Most genome-wide association studies have been of people of European descent.



NIH-Funded Pulmonary Publications 1993-2013



95% of study populations are of European origin





Making Precision Medicine

Socially Precise

What is asthma?

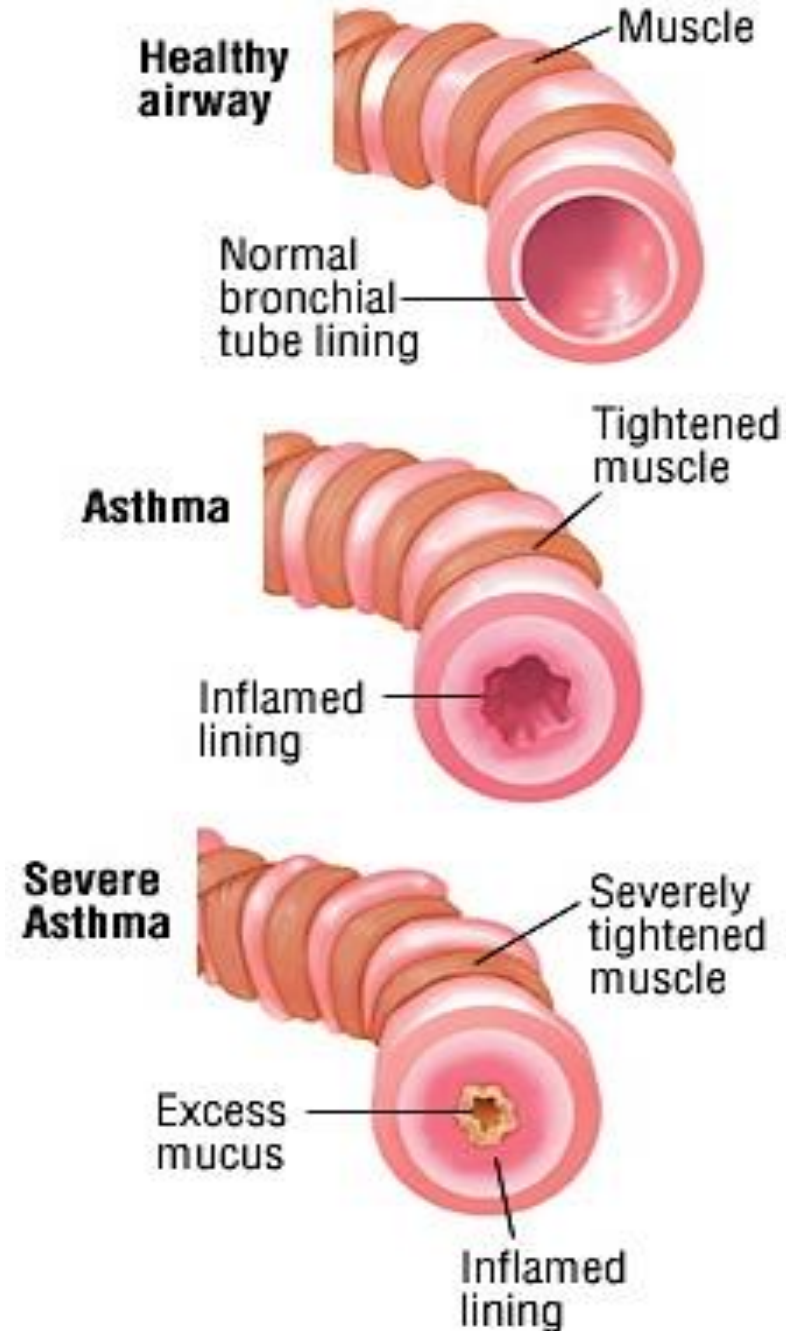
Tightening of Airways

Airway Remodeling

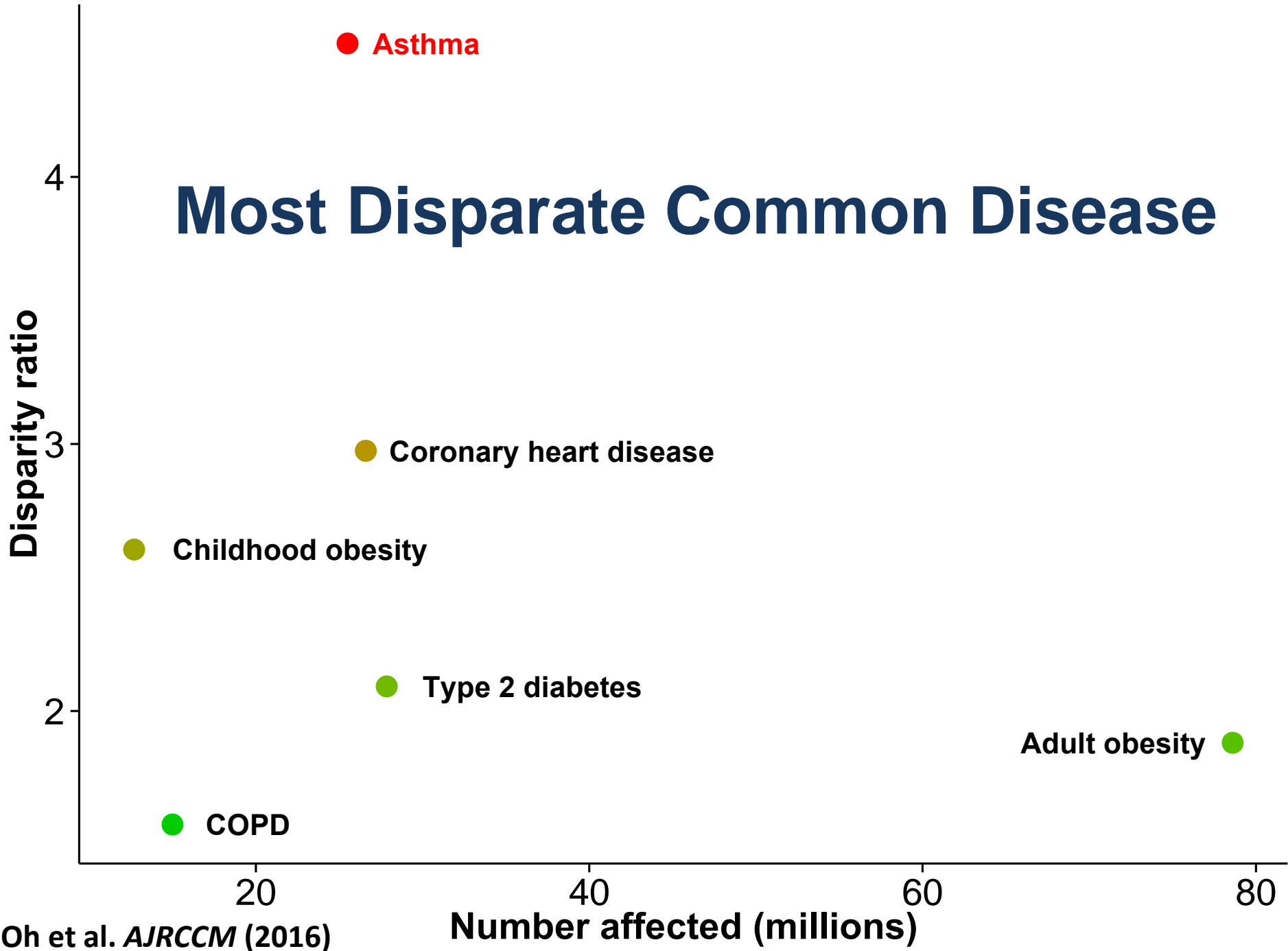
Thick Mucous Production

Acute and Chronic

- Wheezing
- Coughing
- Shortness of Breath

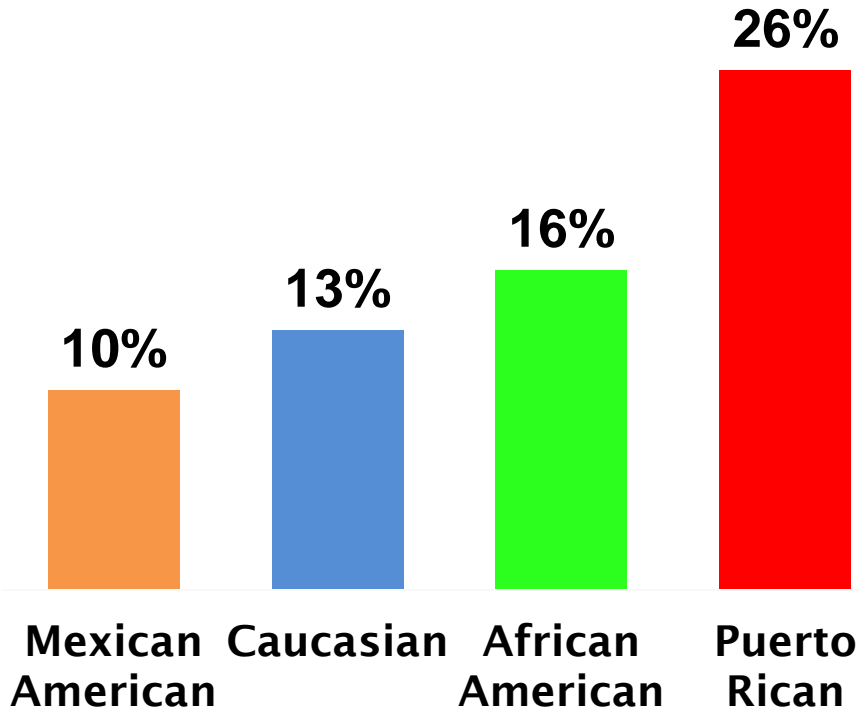


Most Disparate Common Disease



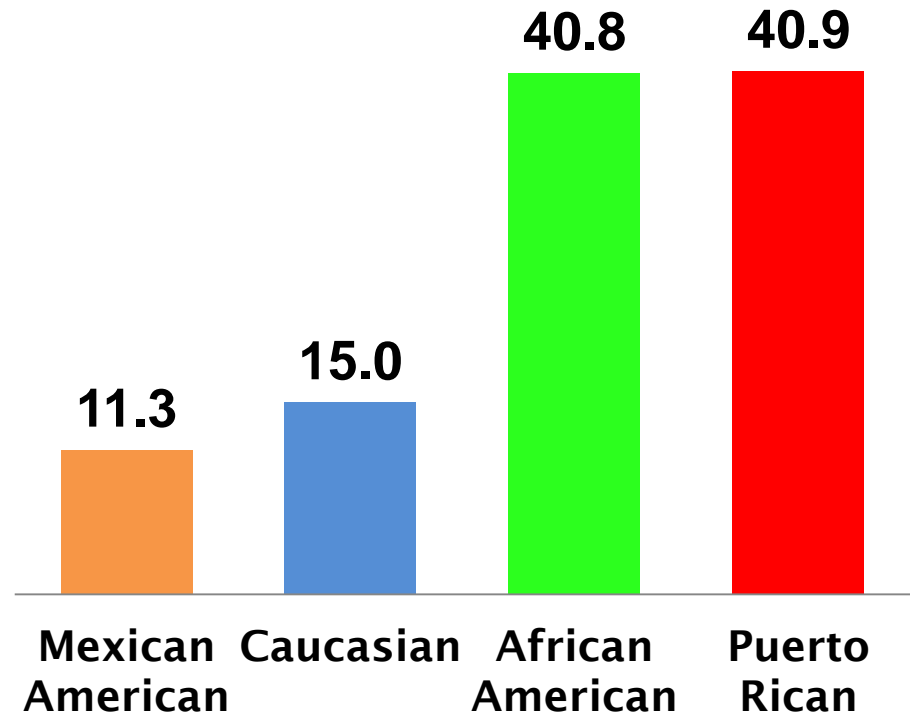
Asthma Affects ~334M Globally

Prevalence



Lara M et al. Pediatrics (2006).

Mortality



Homa DM et al. Am. J. Respir. Crit. Care Med. (2000)

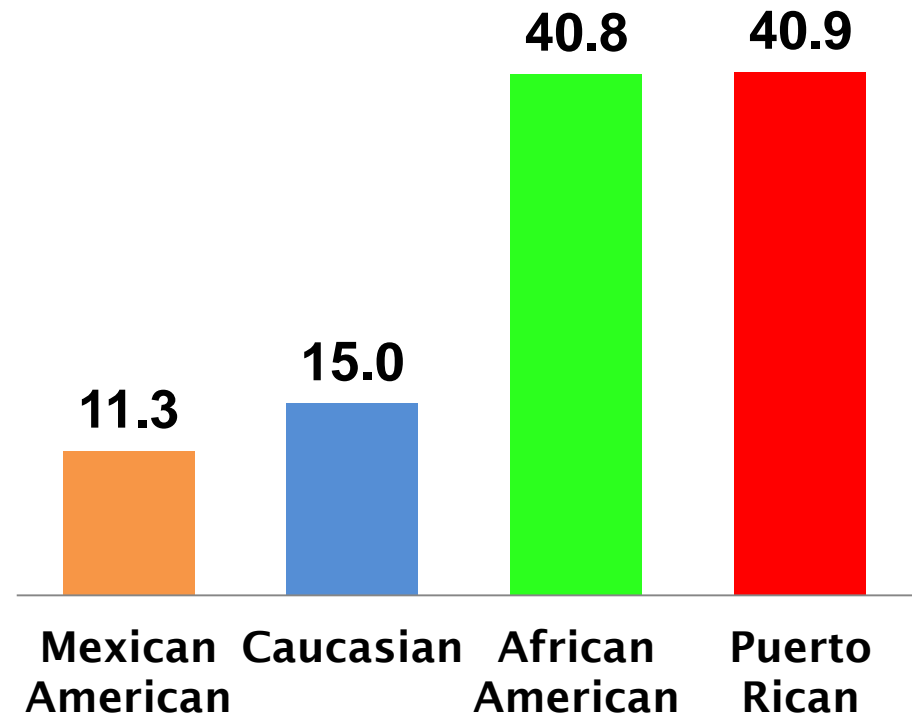
Asthma Affects ~334M Globally

Genetics

Mortality

vs.

Environment?



Homa DM et al. Am. J. Respir. Crit. Care Med. (2000)

**Recruited > 10,000 minority
participants**

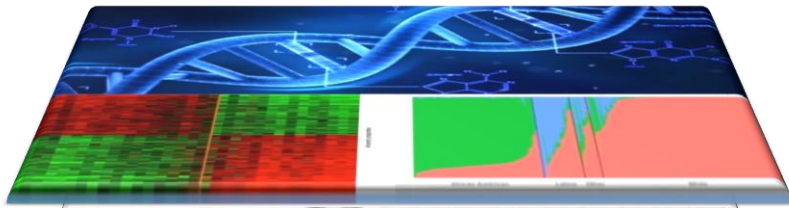
GALA & SAGE STUDIES

Local, national, international



1998 - present

UCSF



Genomic



Clinical



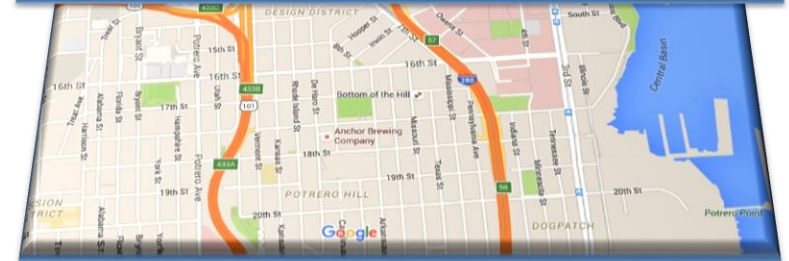
Behavioral



Socio-demographic



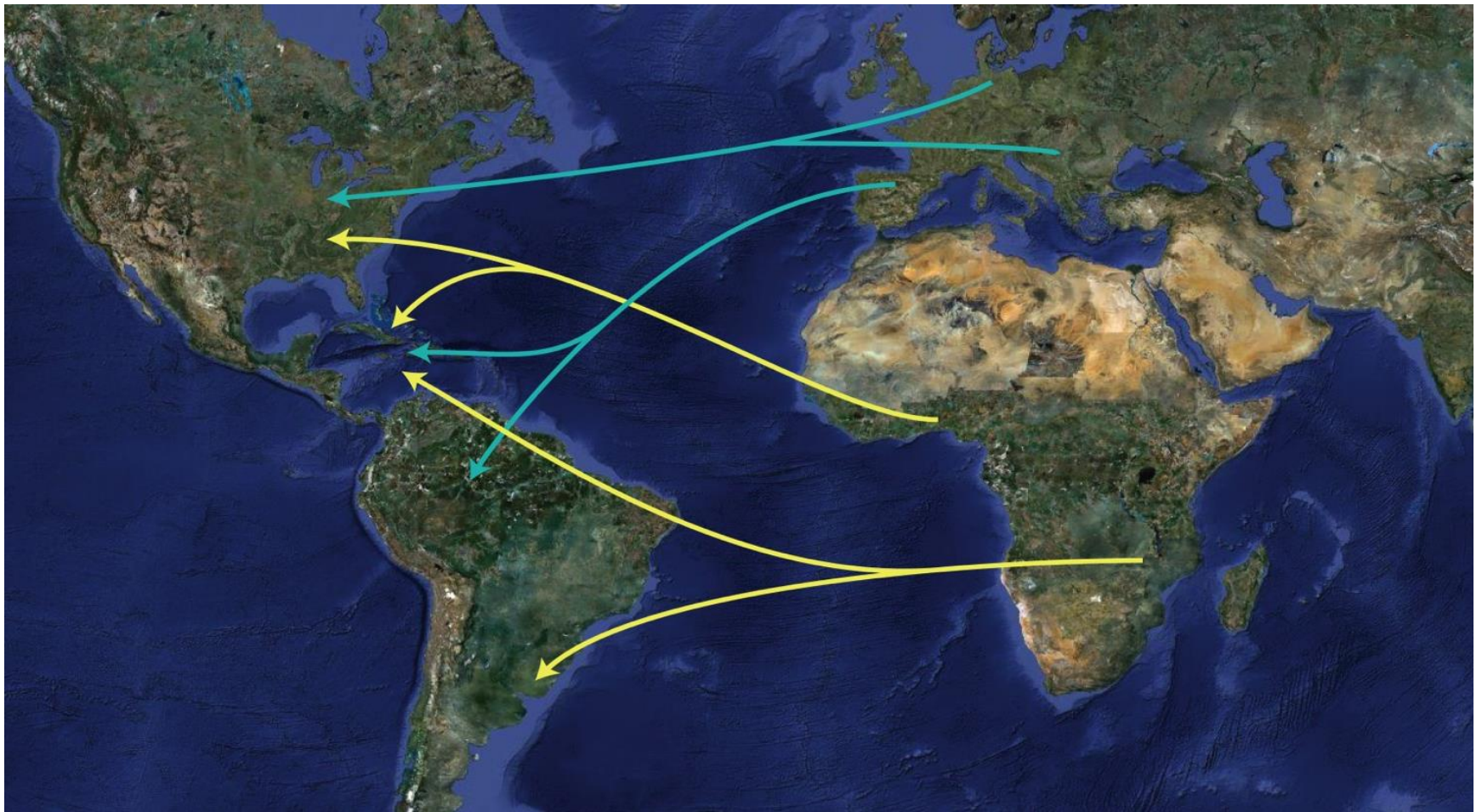
Built environment



Geographic

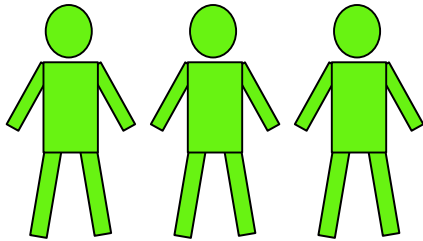
Racially Mixed Populations

Rich resource for study of complex diseases

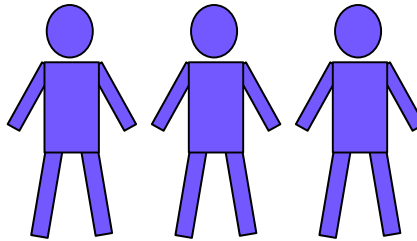


Ancestry of Latinos & African Americans

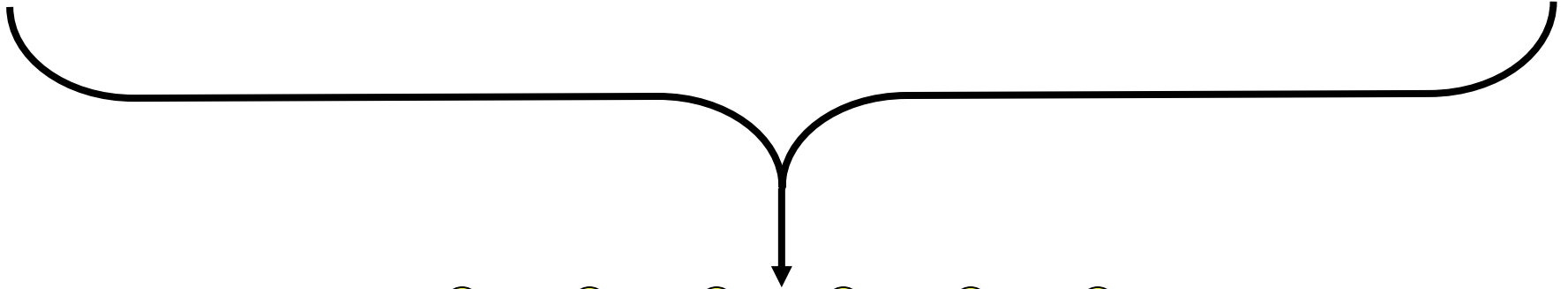
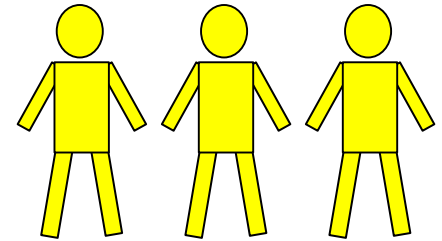
African



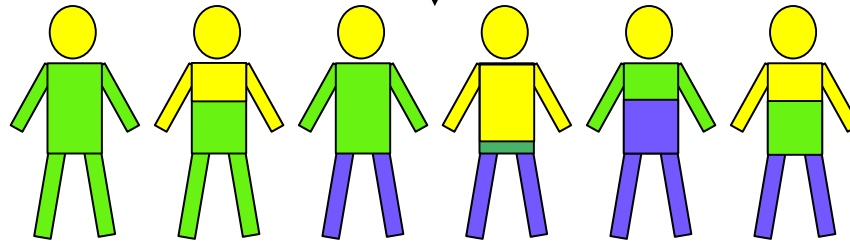
Native American



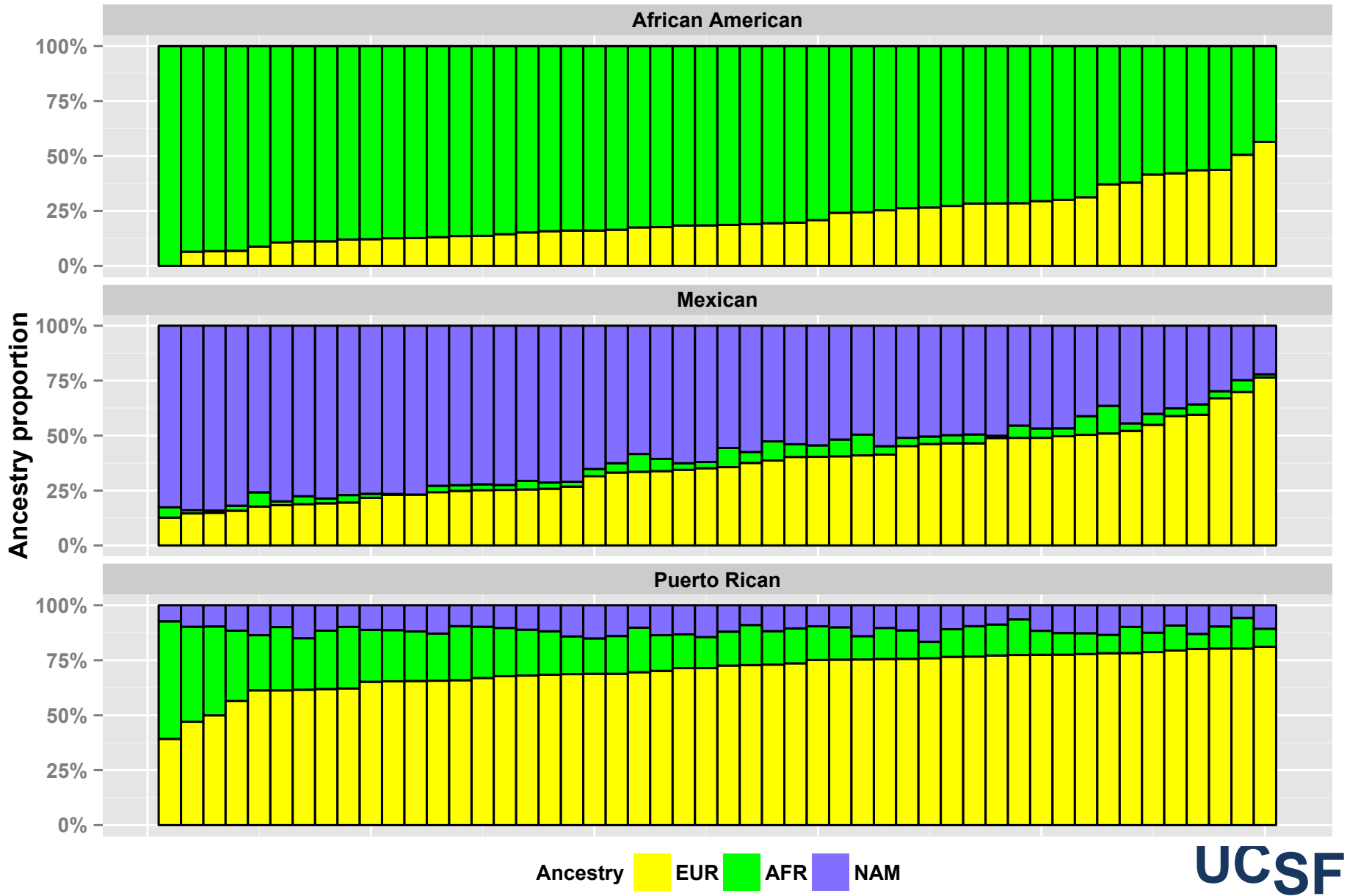
European



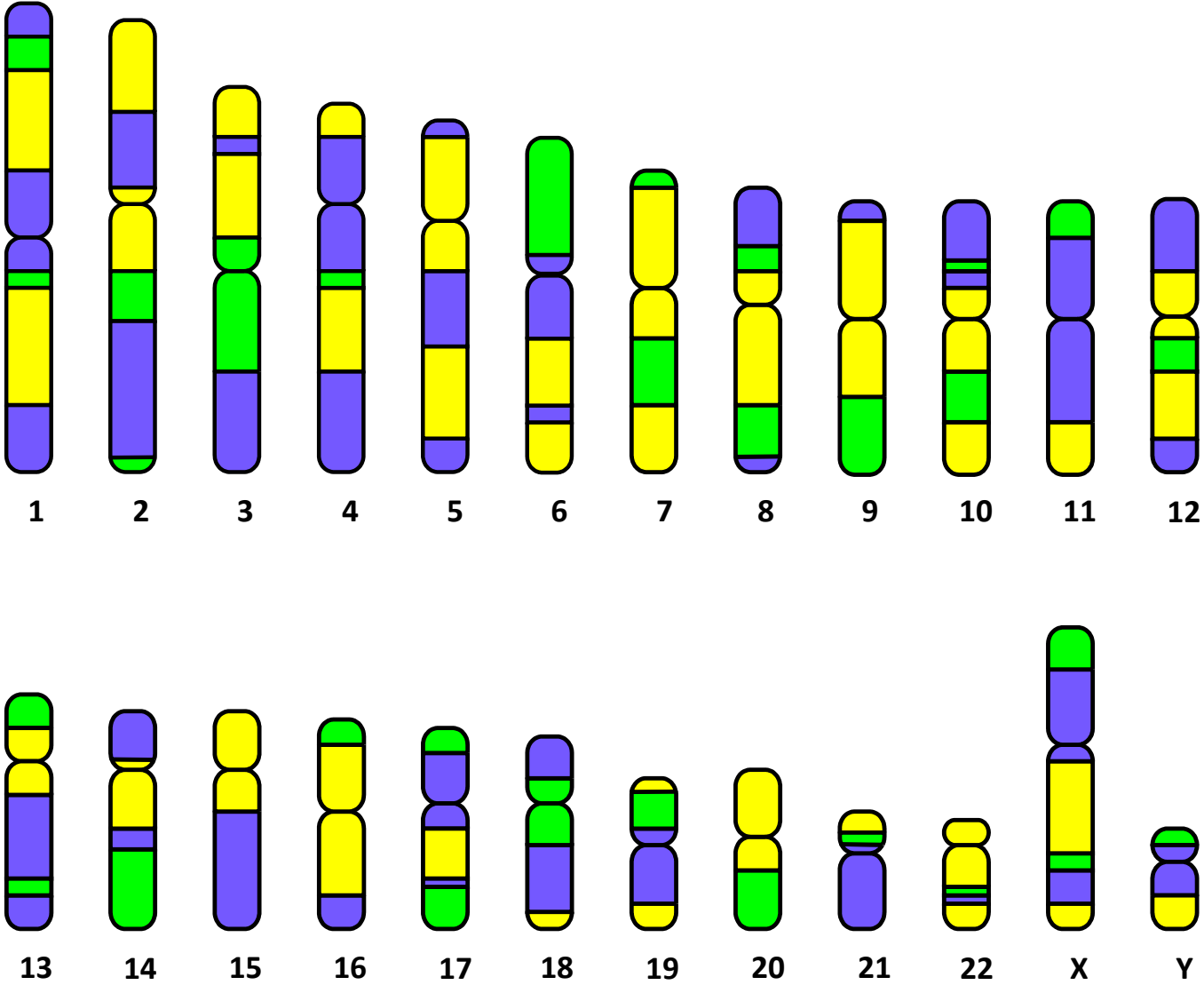
Admixed



Global Ancestry



Locus Specific *Ancestry*

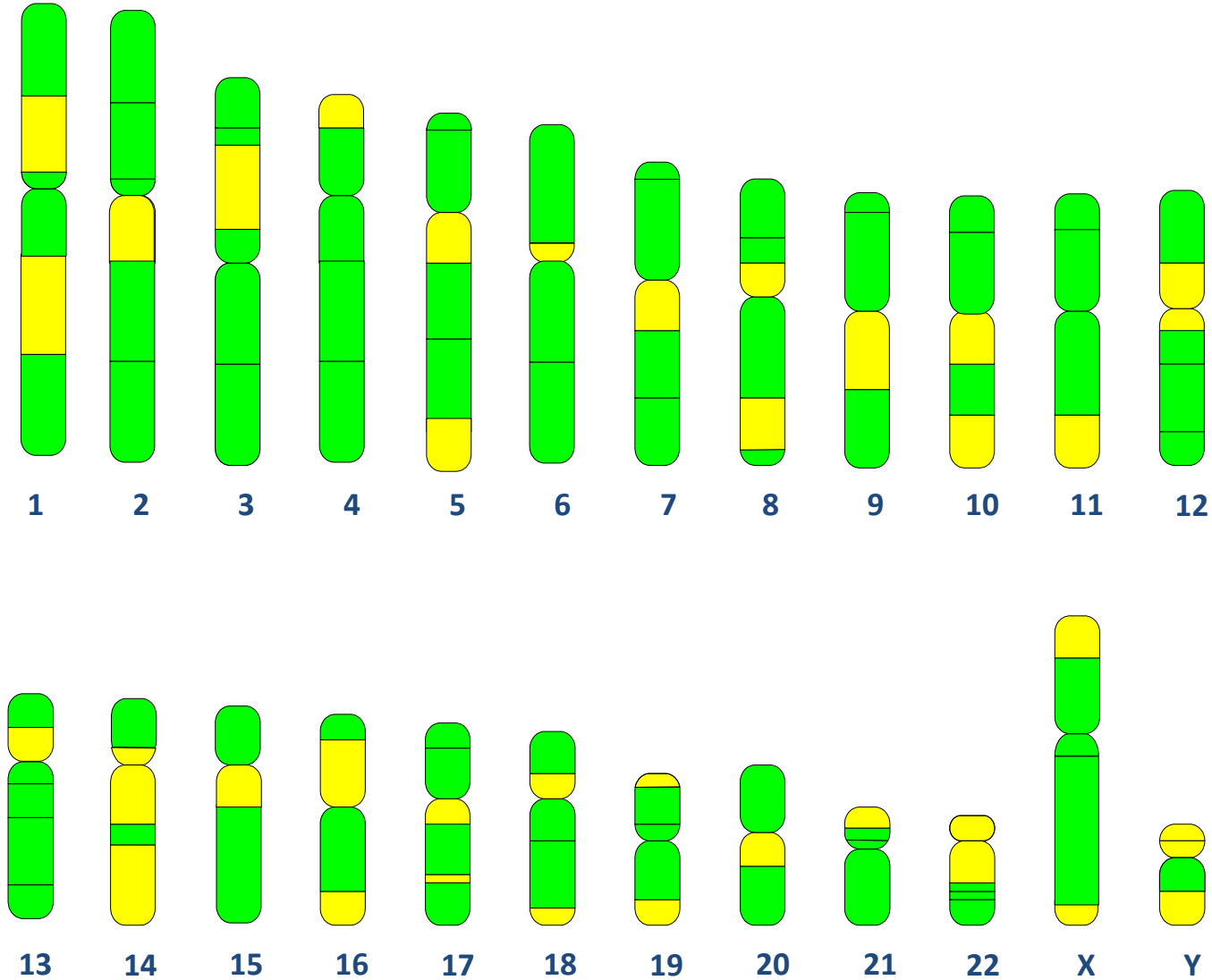


Can We Leverage *Genetic Ancestry*

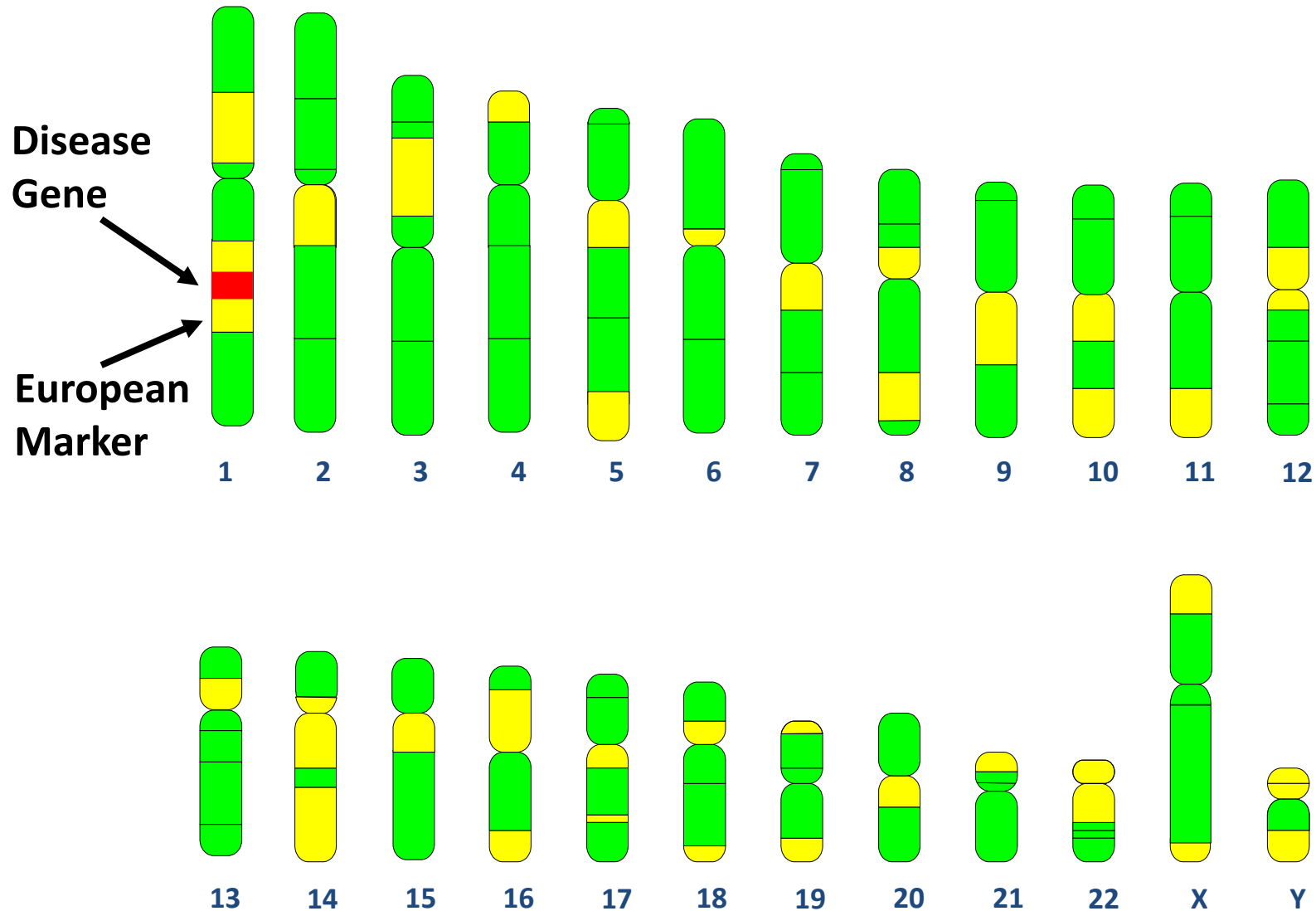
to

Scientific Advantage?

African Americans & Multiple Sclerosis



African Americans & Multiple Sclerosis

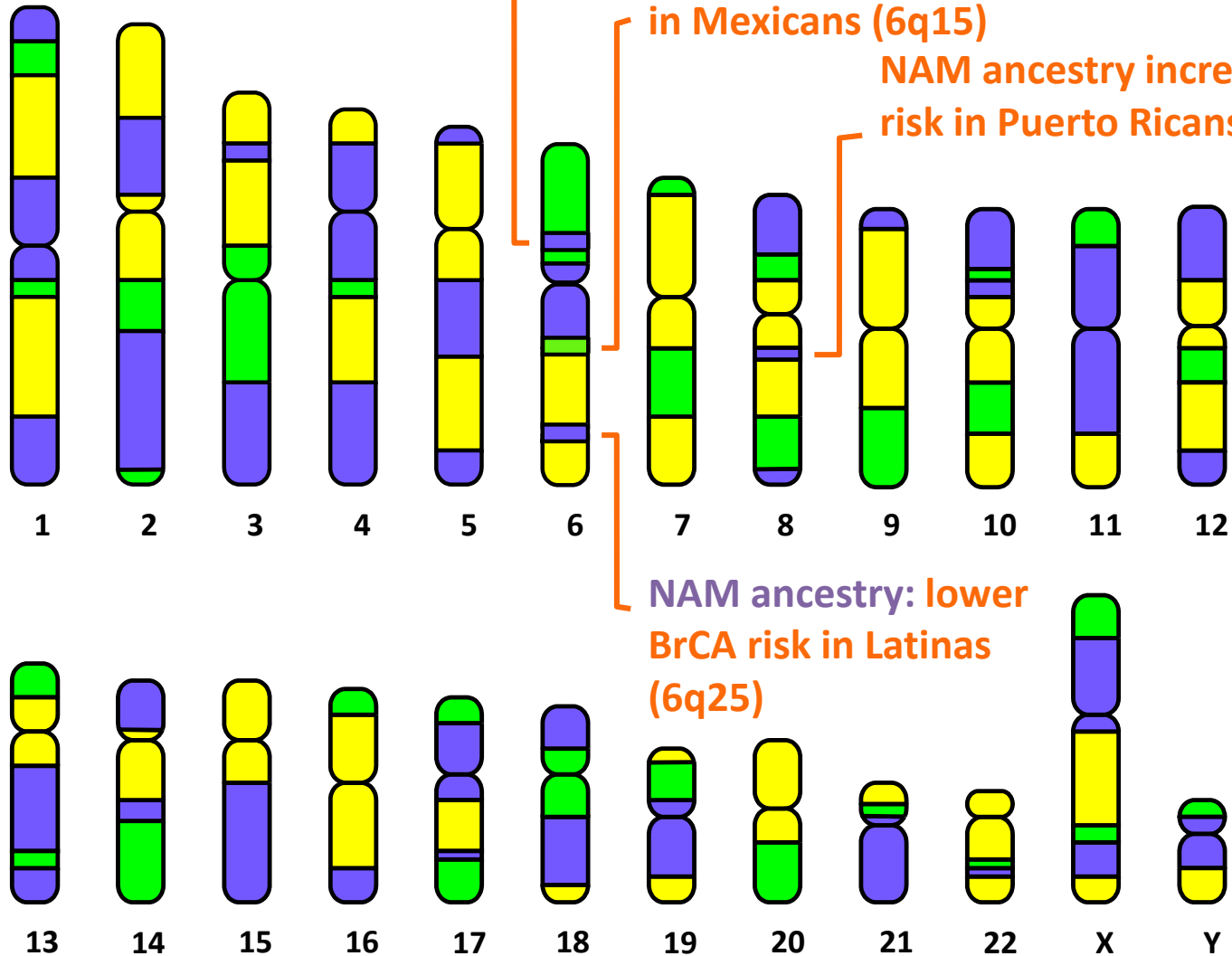


Locus Specific *Ancestry*

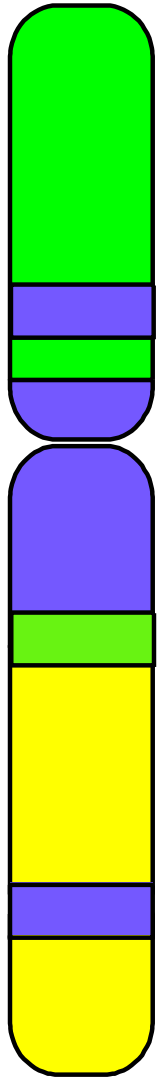
NAM ancestry: lower IgE levels in Latinos (6p21)

AFR ancestry: protective for asthma in Mexicans (6q15)

NAM ancestry increases asthma risk in Puerto Ricans (8q12)



Locus Specific *Ancestry*



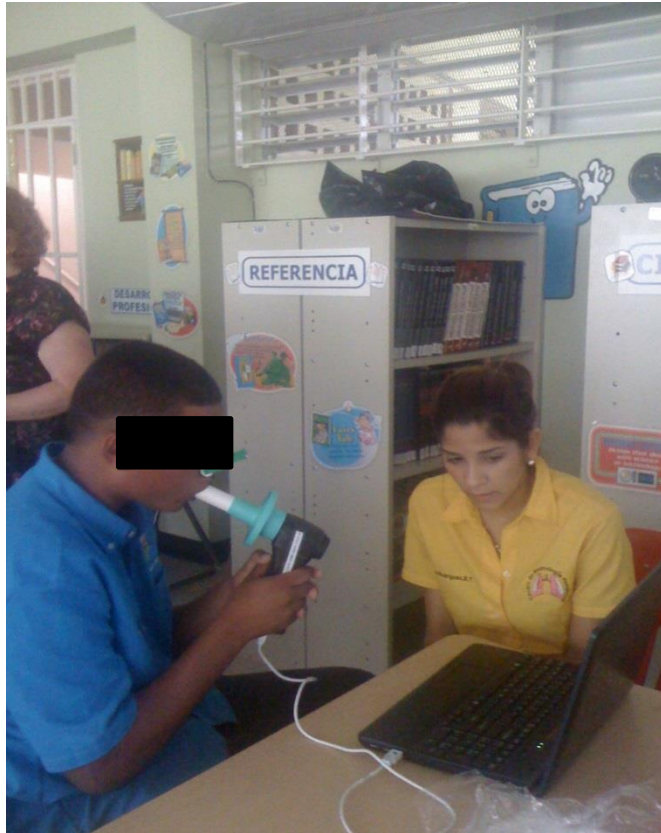
NAM ancestry: lower IgE levels in Latinos (6p21)

AFR ancestry protective for asthma in Mexicans (6q15)

NAM ancestry: lower BrCA risk in Latinas (6q25)

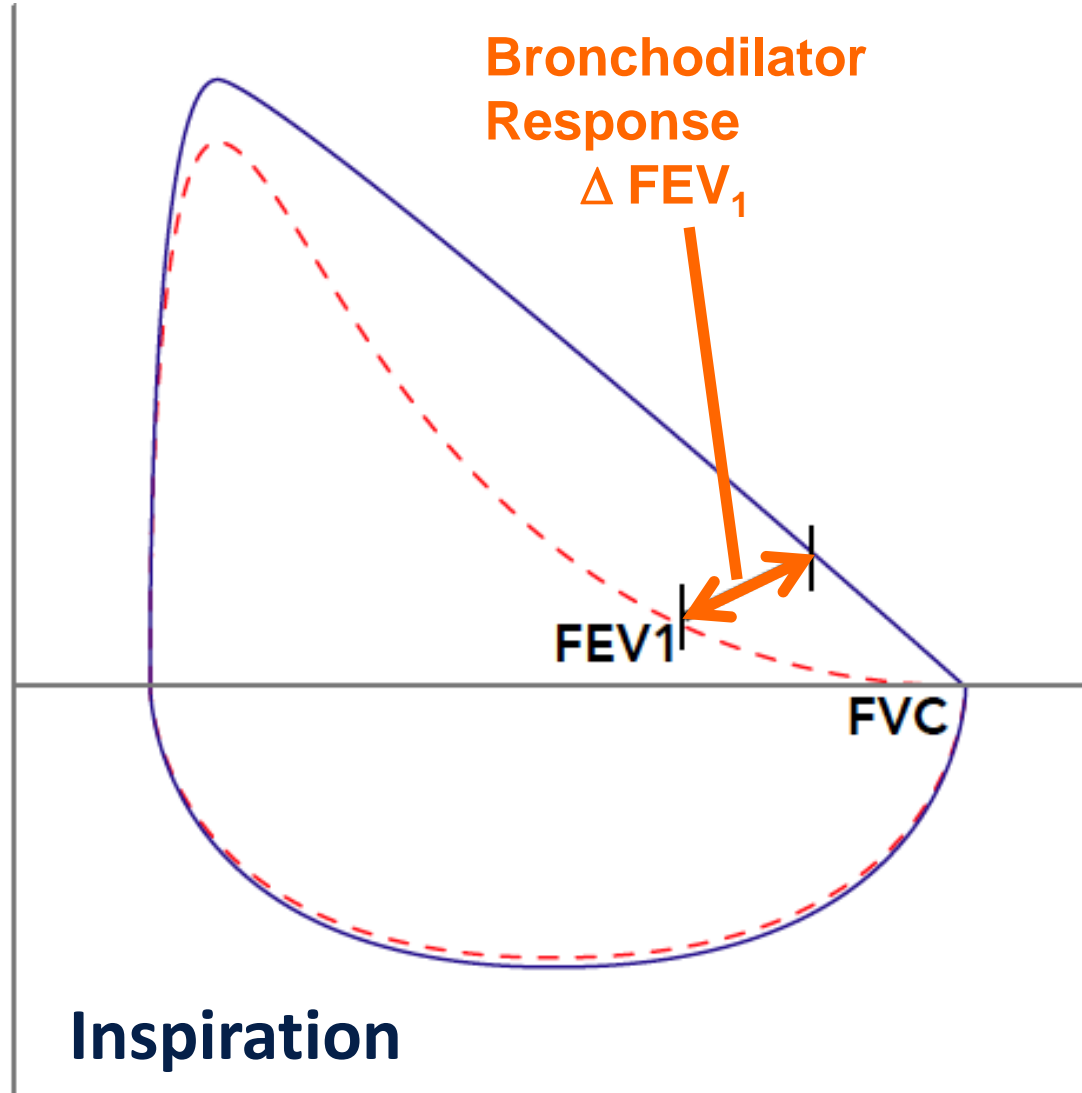
6

Measuring Bronchodilator Response

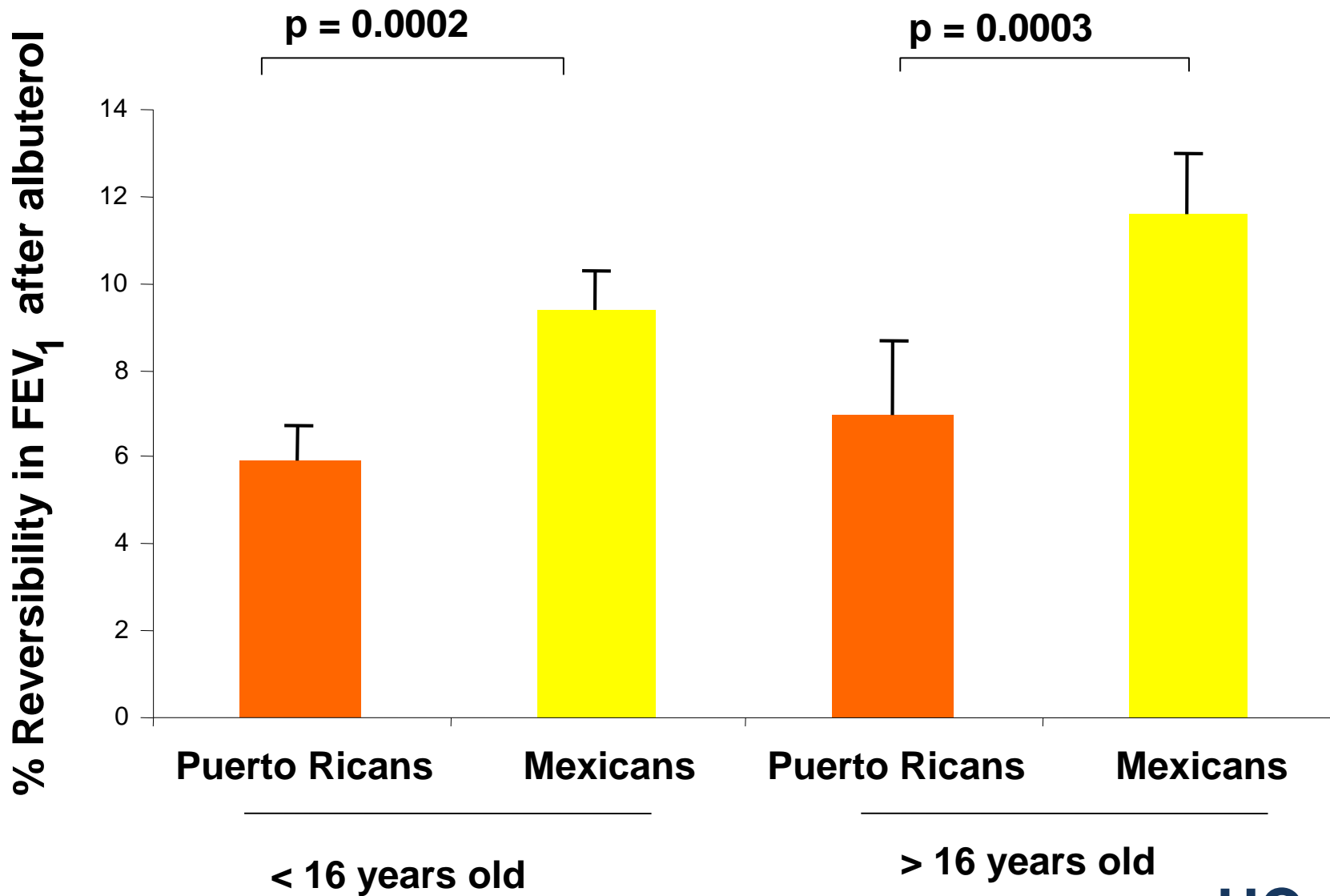


Exhalation

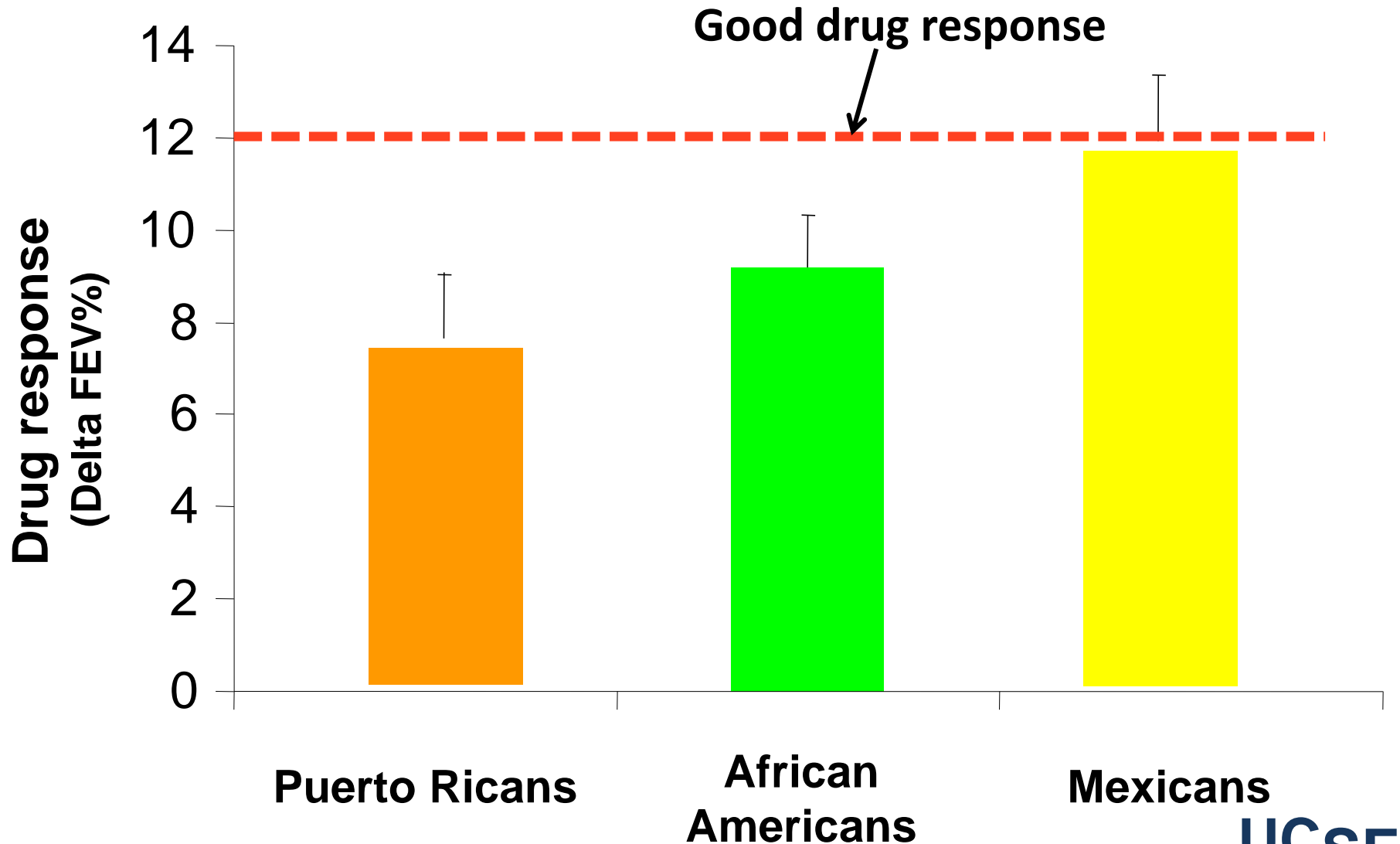
Flow (L/s)



Ethnicity & Drug Response



Children with Moderate-to-Severe Asthma



Black Box Warning

**“In African Americans,
asthma-related deaths occurred at a
higher rate in patients treated with
Salmeterol than those treated with
placebo (..relative risk: 7.26..)...”**

Whole genome sequencing study on bronchodilator response in minority children

UCSF Asthma Collaboratory

UCSF



UCSF



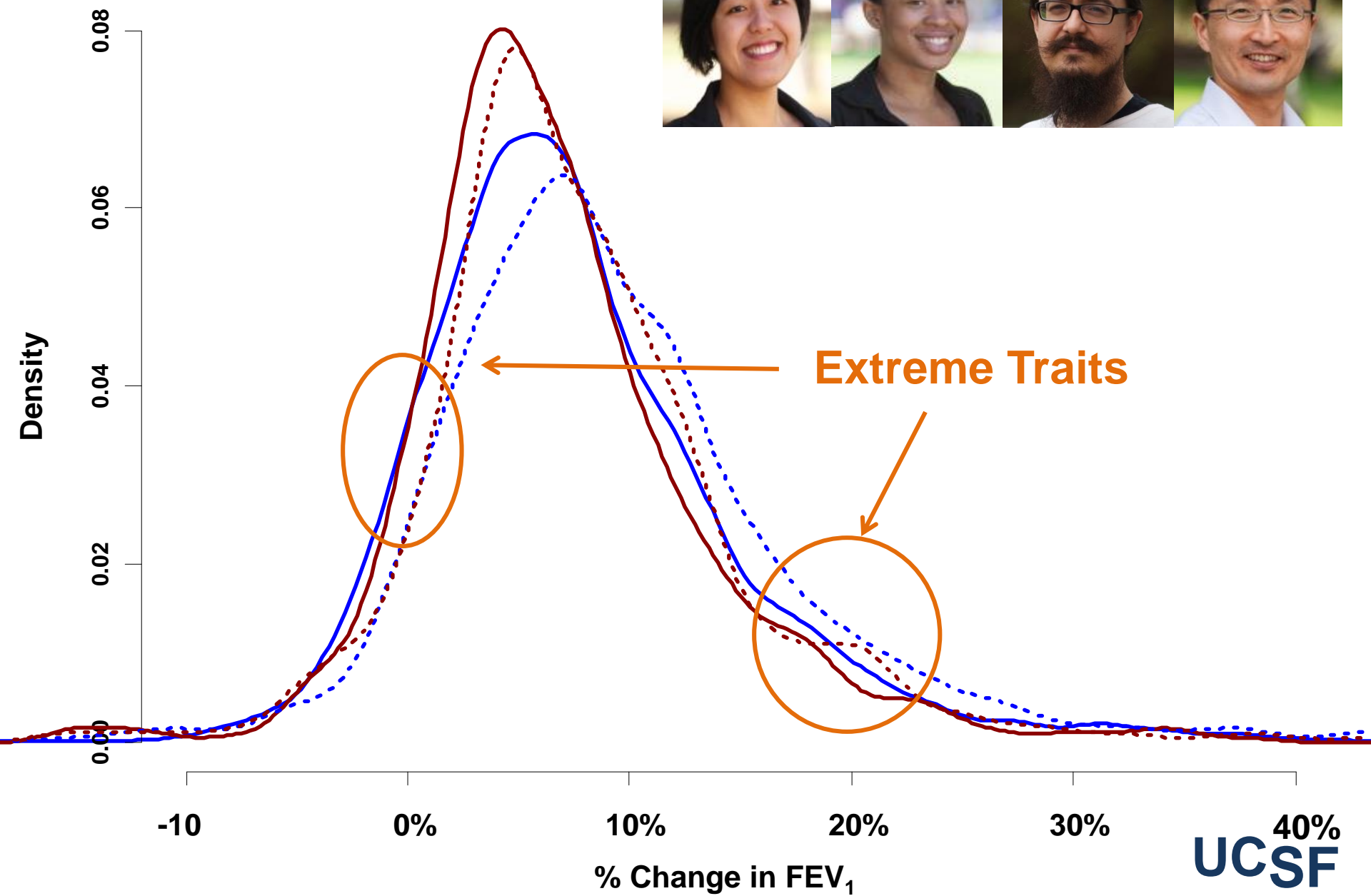


National Heart, Lung,
and Blood Institute

Whole genome sequencing

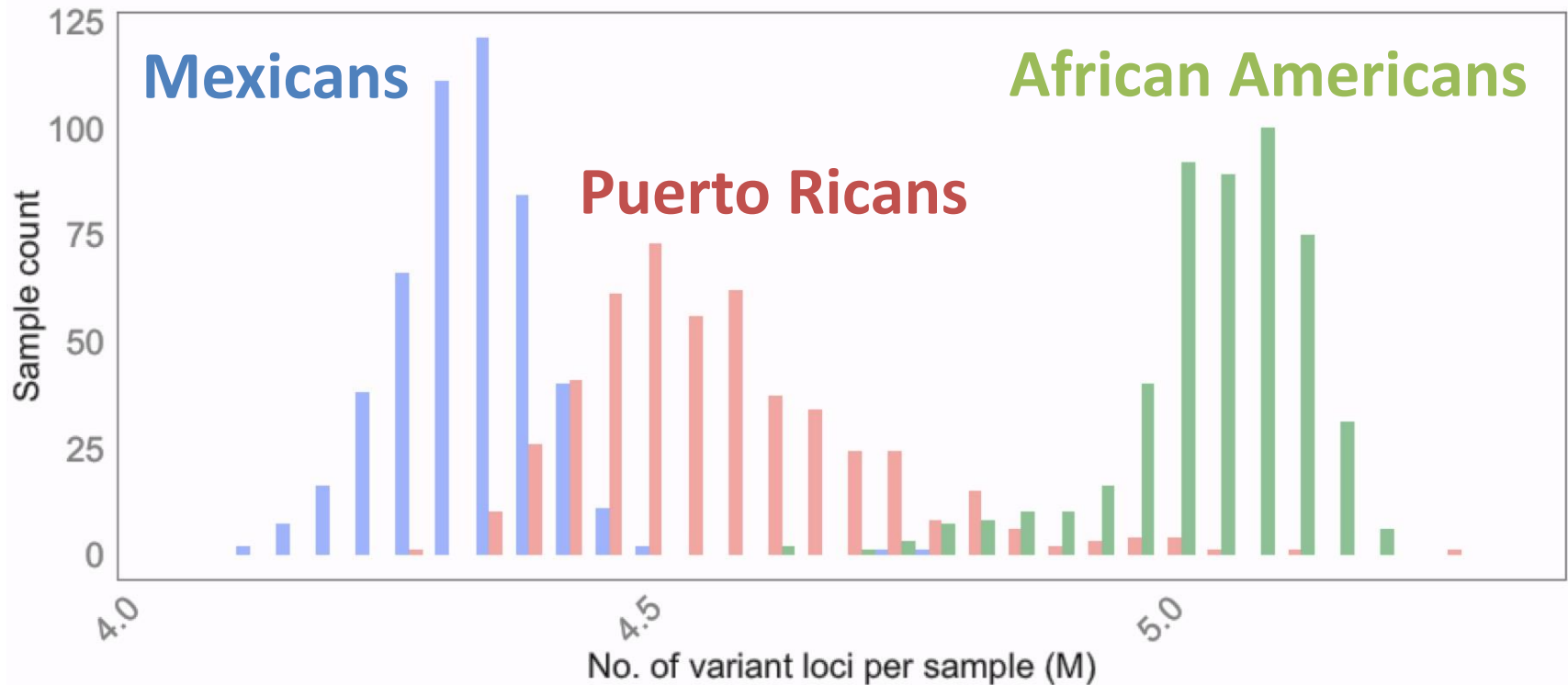
1,500 minority children

Albuterol response



Extreme Traits

4.1 – 5.3 million variants/sample



66 million loci jointly called in 1484 samples
(PASS FILTER)

BDR Association

$$\mathbf{BDR} = \text{Variants} + \text{Age} + \text{Sex} + \text{BMI} + \begin{matrix} \text{Global} \\ \text{Ancestry} \end{matrix}$$

Individual effects

- PLINK
- Common variants
 - $\text{MAF} > 1\%$
- Logistic regression

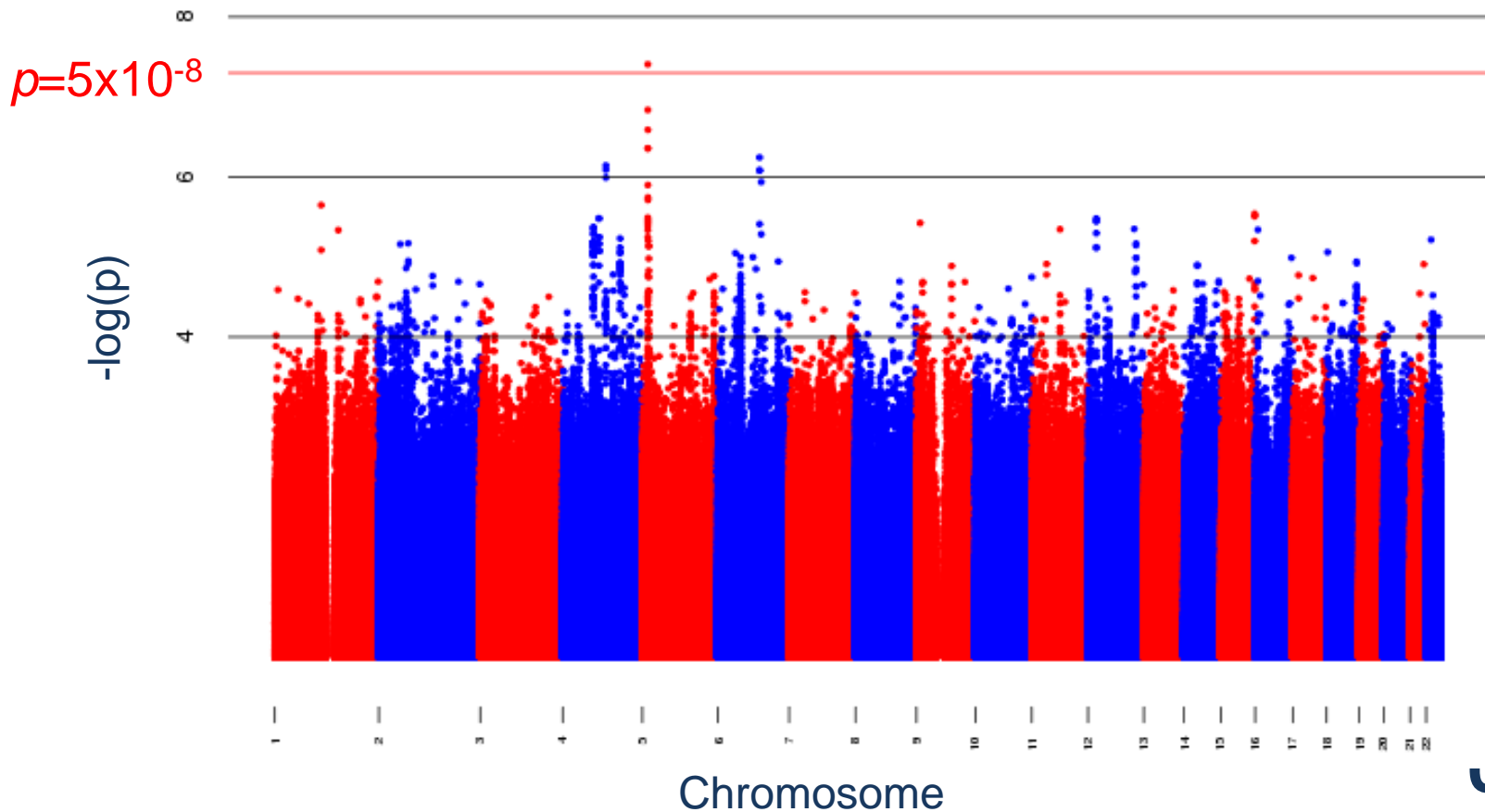
Combined effects

- SKAT-O
- Rare variants
- Group variants by sliding windows

Cosmopolitan, Common Variants

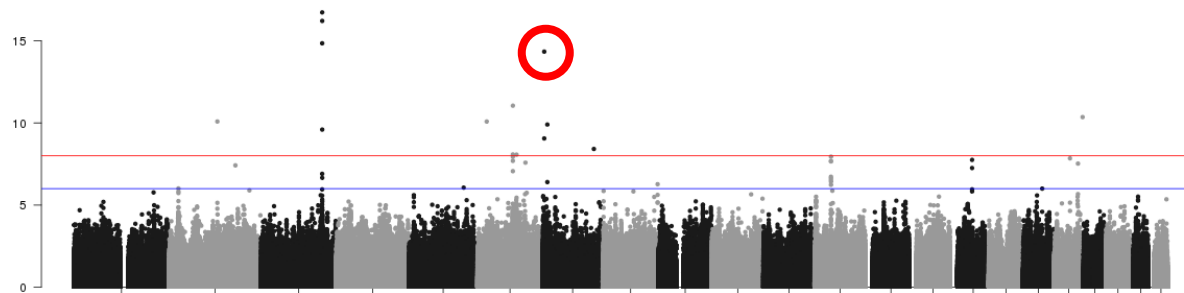
CTNND2/DNAH5 (Intergenic)

$p=3.91E-08$, OR=1.62



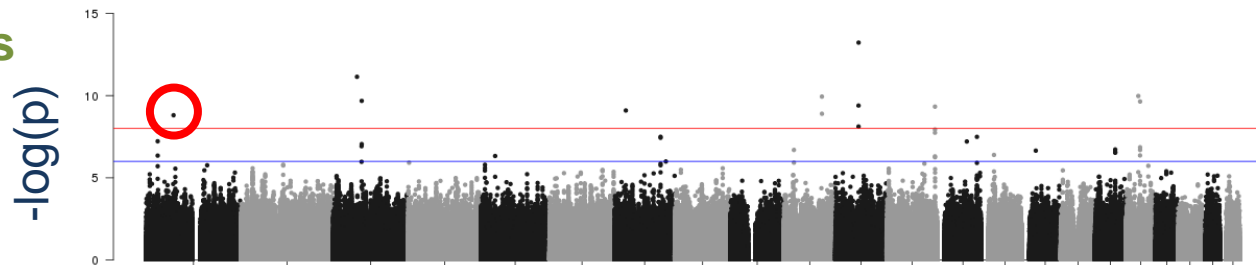
Ethnic-specific Rare Variants, Combined Effects

Puerto Ricans



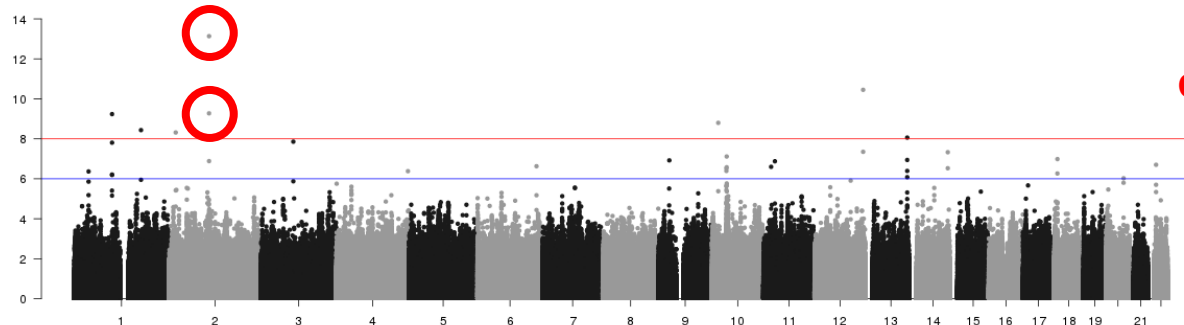
chr7 FO XK1

African Americans



chr1 NEGR1

Mexican



chr2 FHL2, KCNS3

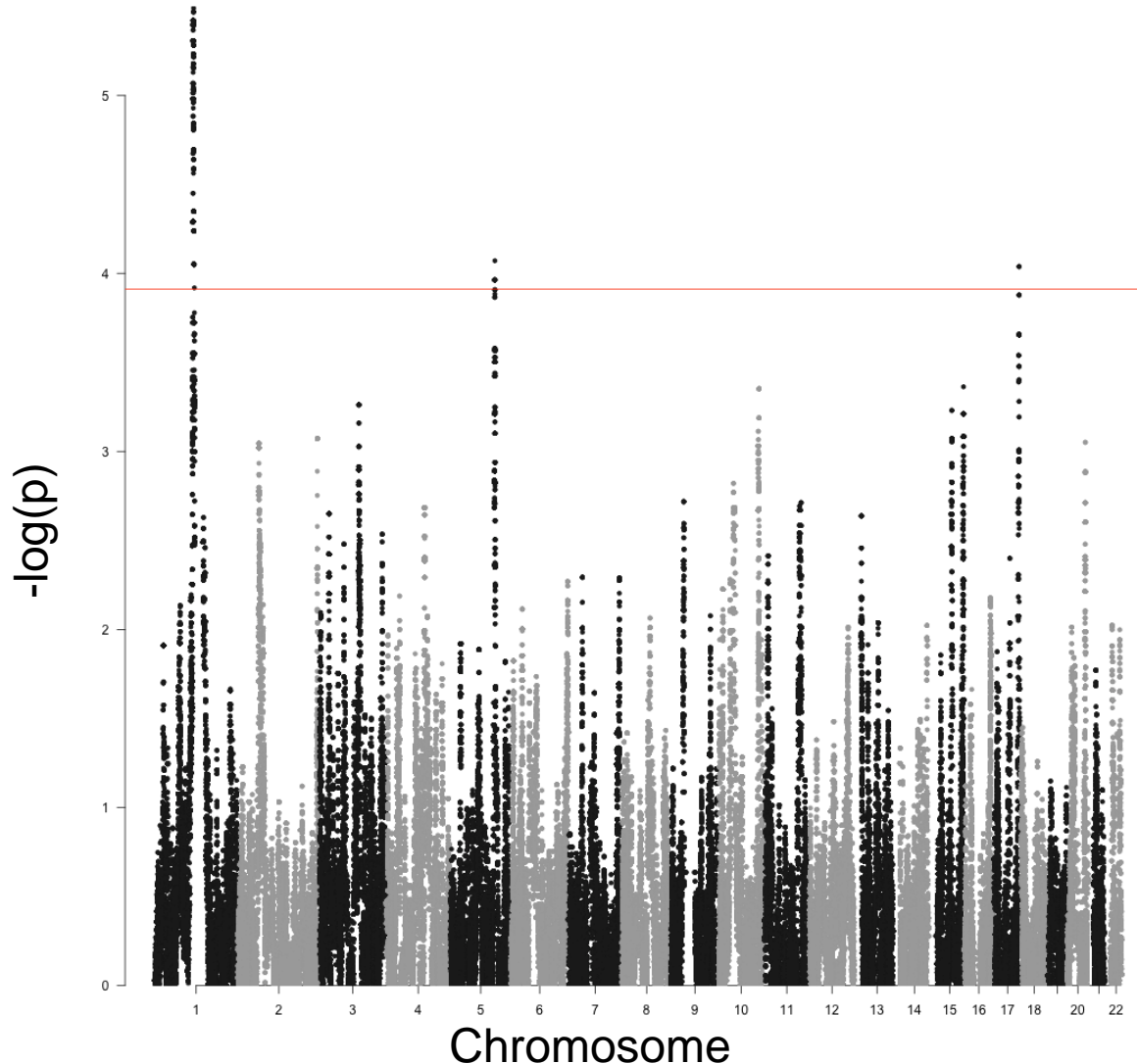
Chromosome

SKAT-O, 5kb sliding window, step of 500 bp

UCSF

Ancestry-specific BDR Association

Native American Ancestry (Puerto Ricans)



Chr1

CD2

CD58

SLC22A15

VANGL1

Top BDR Genes & Clinical Traits

Lung
capacity

COPD

DNAH5

Corticosteroids /
BDR

FOKK1
SLC22A15

Airway hyper-
responsiveness

FHL2
KCNS3
VANGL1

T-cell
stimulation

CD2
CD58

BDR WGS Summary

- **Racial differences in Drug Response**
- **WGS = novel, ethnic-specific associations**
 - Impossible to identify with array data alone

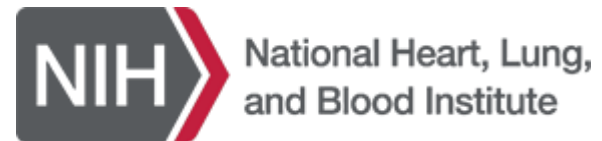
Team Science



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TOPMed

