



# Precision medicine and ethnic labeling of genetic variants

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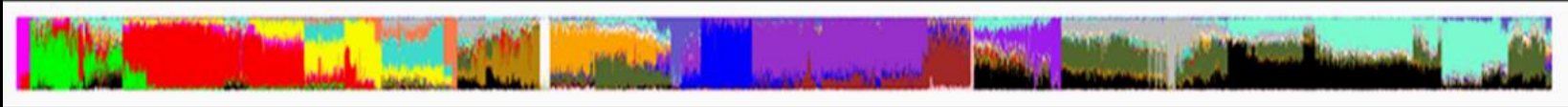
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# Genome-wide genotype and sequence-based reconstruction of the 140,000 year history of modern human ancestry

Daniel Shriner, Fasil Tekola-Ayele, Adebowale Adeyemo &amp; Charles N. Rotimi

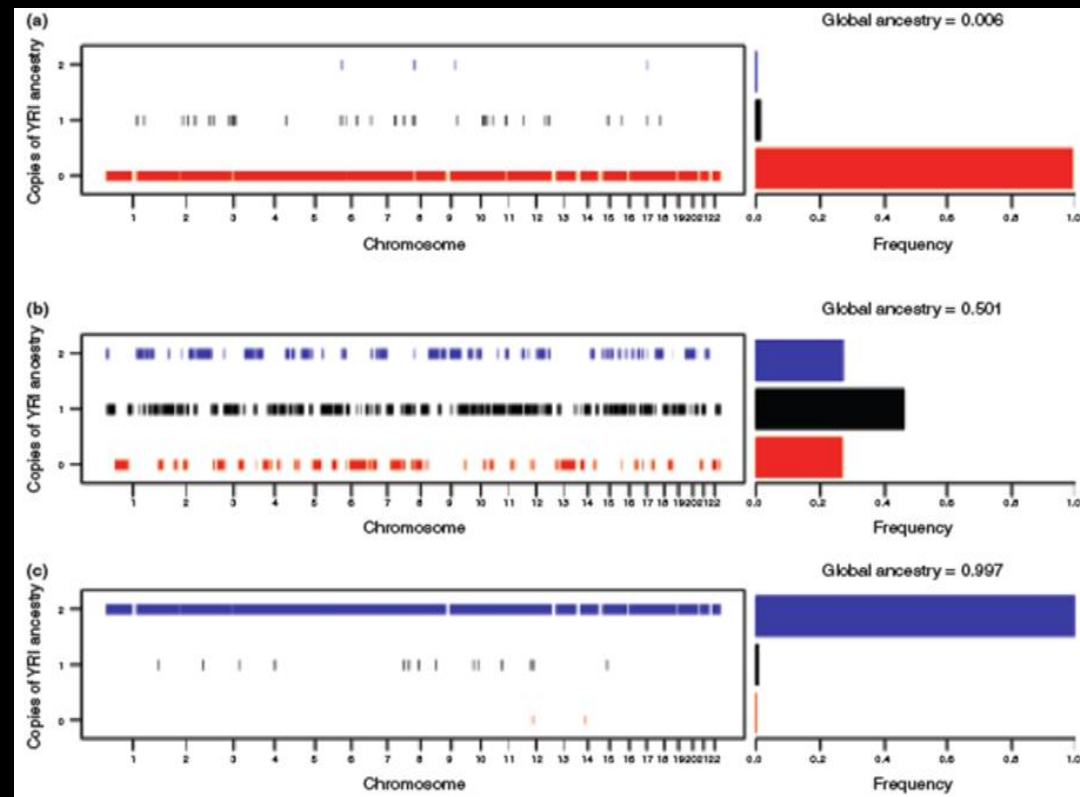
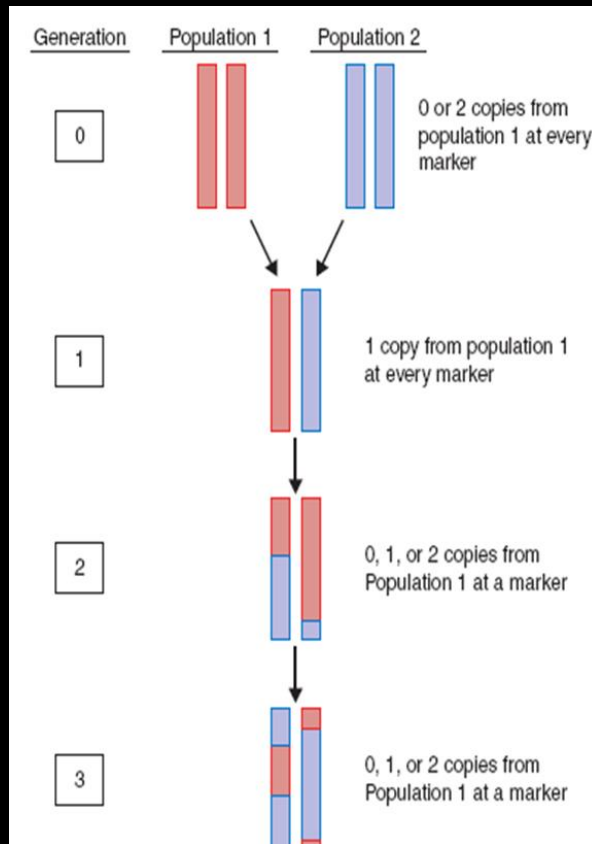
Center for Research on Genomics and Global Health, National Human Genome Research Institute, Building 12A, Room 4047, 12 South Drive, Bethesda, Maryland 20892 USA.

1. Investigated ancestry of 3,528 modern humans (163 ethno-linguistic groups)
2. 19 ancestral components
3. 94.4% of individuals showed mixed ancestry



4. Refined understanding of the ancestry of several ethno-linguistic groups, including African Americans, Ethiopians, the Kalash, Latin Americans, Mozabites, Pygmies, and Uygurs, as well as the CEU sample.
5. **Ubiquity of mixed ancestry emphasizes the importance of accounting for ancestry in history, forensics, and health.**

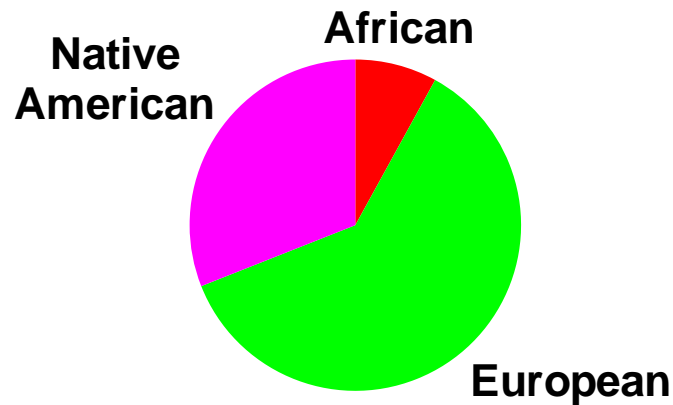
# Mapping of disease-associated variants in admixed populations



Self identified African Americans includes individuals with as low as 0.6% to as high as 99.7% African ancestry – Average is ~80%

# Individual ancestry is more informative than ethnicity

## HISPANIC

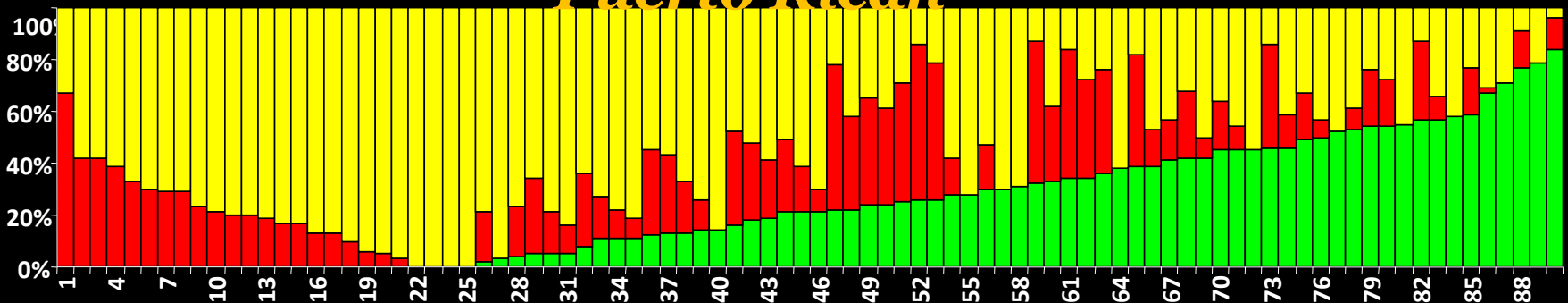


Mexican



Puerto Rican

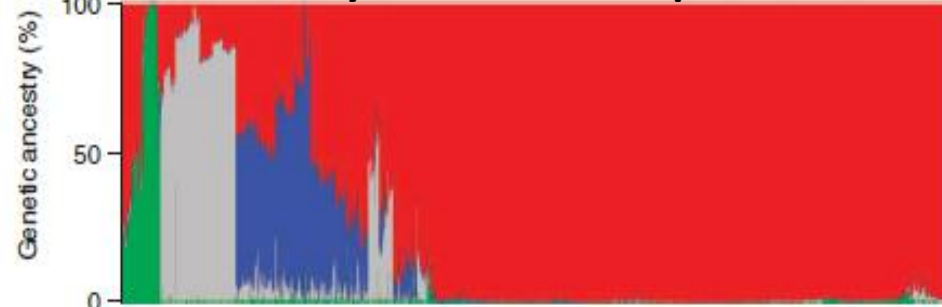
## *Puerto Rican*



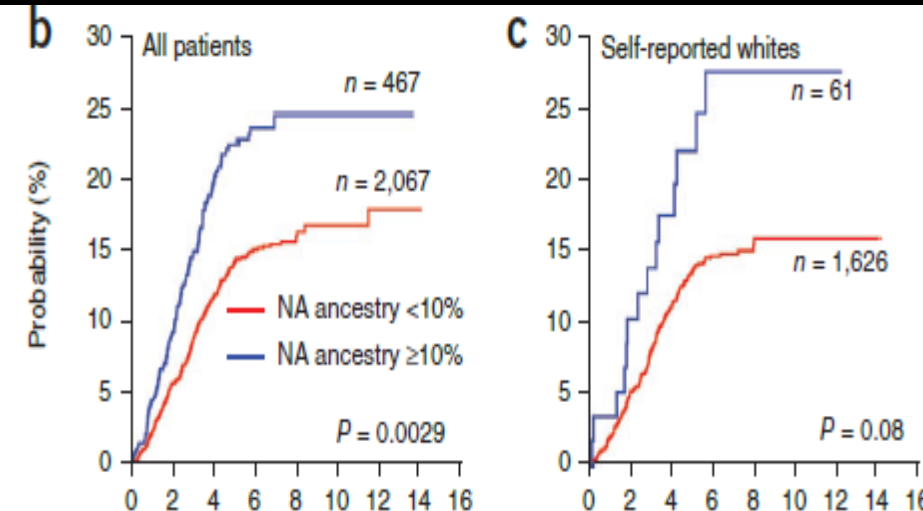
# Ancestry and pharmacogenomics of relapse in acute lymphoblastic leukemia

Jun J Yang<sup>1</sup>, Cheng Cheng<sup>2</sup>, Meenakshi Devidas<sup>3</sup>, Xueyuan Cao<sup>2</sup>, Yiping Fan<sup>4</sup>, Dario Campana<sup>5</sup>, Wenjian Yang<sup>1</sup>,

**a** Genetic ancestry and risk of relapse . N=2,534



Euro=red; African=gray; Asian=green; NA=blue



Five-year survival rates for Childhood acute lymphoblastic leukemia (ALL) is over 80% in industrialized countries. Not all children have benefited equally from the progress. Ethnic difference in survival is well known.

Using whole genome approach, it was shown that the component of genomic variation that co-segregate with Native American ancestry was associated with risk of relapse ( $p=0.0029$ ).

Importantly, ancestry-related risk of relapse was mitigated by the addition of single extra phase of chemotherapy.

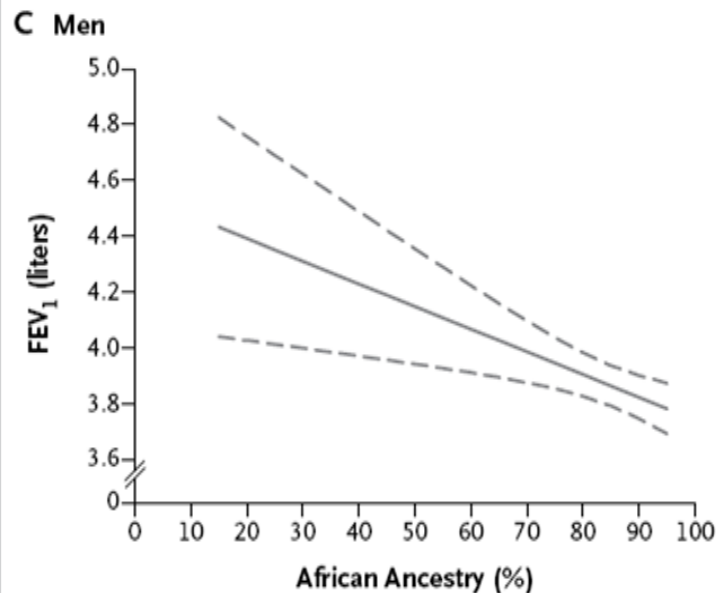


# Genetic Ancestry in Lung-Function Predictions

Rajesh Kumar, M.D., Max A. Seibold, Ph.D., Melinda C. Aldrich, Ph.D., M.P.H.,

## RESULTS

African ancestry was inversely related to forced expiratory volume in 1 second ( $FEV_1$ ) and forced vital capacity in the CARDIA cohort. These relations were also seen in the HABC and CHS cohorts. In predicting lung function, the ancestry-based model fit the data better than standard models. Ancestry-based models resulted in the reclassification of asthma severity (based on the percentage of the predicted  $FEV_1$ ) in 4 to 5% of participants.



## CONCLUSIONS

Current predictive equations, which rely on self-identified race alone, may misestimate lung function among subjects who identify themselves as African American. Incorporating ancestry into normative equations may improve lung-function estimates and more accurately categorize disease severity. (Funded by the National Institutes of Health and others.)

# Genetic variation in *IL28B* predicts hepatitis C treatment-induced viral clearance

Dongliang Ge<sup>1</sup>, Jacques Fellay<sup>1</sup>, Alexander J. Thompson<sup>2</sup>, Jason S. Simon<sup>3</sup>, Kevin V. Shianna<sup>1</sup>, Thomas J. Urban<sup>1</sup>, Erin L. Heinzen<sup>1</sup>, Ping Qiu<sup>3</sup>, Arthur H. Bertelsen<sup>3</sup>, Andrew J. Muir<sup>2</sup>, Mark Sulkowski<sup>4</sup>, John G. McHutchison<sup>2</sup> & David B. Goldstein<sup>1</sup>

1. Hepatitis C virus infection affects 170 million people worldwide; the leading cause of cirrhosis in North America.
2. Treatment - 48-week course of peginterferon-alpha-2b or -alpha-2a combined with ribavirin (RBV).
3. Many patients will not be cured by treatment; Patients of European ancestry have higher probability of being cured than patients of African ancestry.
4. Finding - SNP rs12979860 near the *IL28B* gene, encoding interferon-lambda-3, is associated with ~2-fold change in response to treatment in patients of European ancestry and African-Americans.

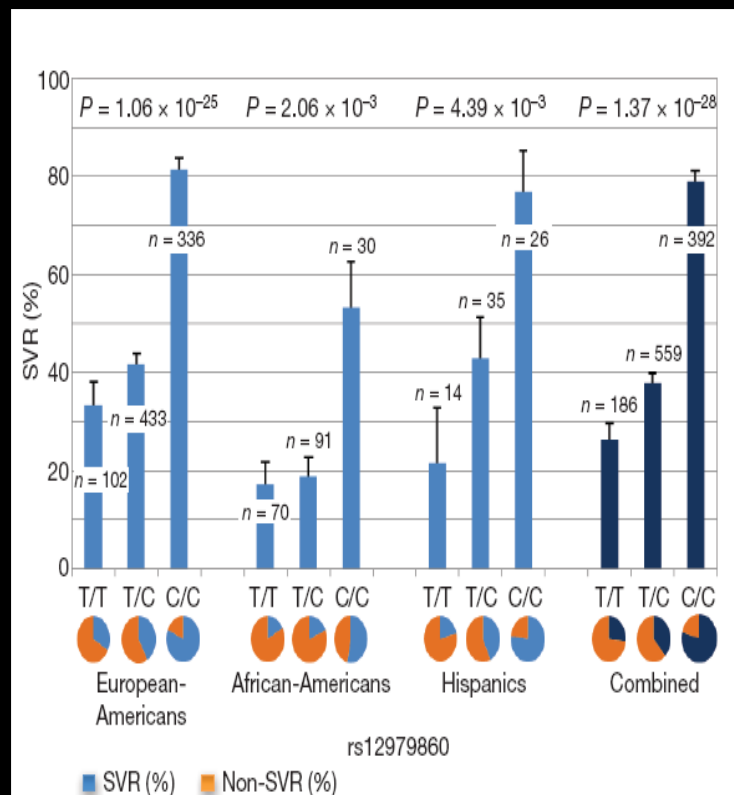


Figure 1 | Percentage of SVR by genotypes of rs12979860. Data are percentages + s.e.m.

SVR – sustained virological response

Nature. Sep 17; 2009.

# Genetic variation in *IL28B* and spontaneous clearance of hepatitis C virus

David L. Thomas<sup>1\*</sup>, Chloe L. Thio<sup>1\*</sup>, Maureen P. Martin<sup>2\*</sup>, Ying Qi<sup>2</sup>, Dongliang Ge<sup>3</sup>, Colm O'hUigin<sup>2</sup>, Judith Kidd<sup>4</sup>, Kenneth Kidd<sup>4</sup>, Salim I. Khakoo<sup>5</sup>, Graeme Alexander<sup>6</sup>, James J. Goedert<sup>7</sup>, Gregory D. Kirk<sup>8</sup>, Sharyne M. Donfield<sup>9</sup>, Hugo R. Rosen<sup>10</sup>, Leslie H. Tobler<sup>11</sup>, Michael P. Busch<sup>11</sup>, John G. McHutchison<sup>12</sup>, David B. Goldstein<sup>3</sup> & Mary Carrington<sup>2,13</sup>

Population Groups	# of individuals (# of populations)	Mean Frequency	Frequency Range
Africa	428 (10)	36.2	23.1 – 54.8
Europe	761 (13)	68.35	52.8 – 85.7
East Asia	380 (8)	94.93	90.0 – 100.0

Because the genotype leading to better response is in substantially greater frequency in European than African populations, this genetic polymorphism also explains approximately half of the difference in response rates between African-Americans and patients of European ancestry

Nature. Sep 17; 2009.

Nature – Oct 8, 2009

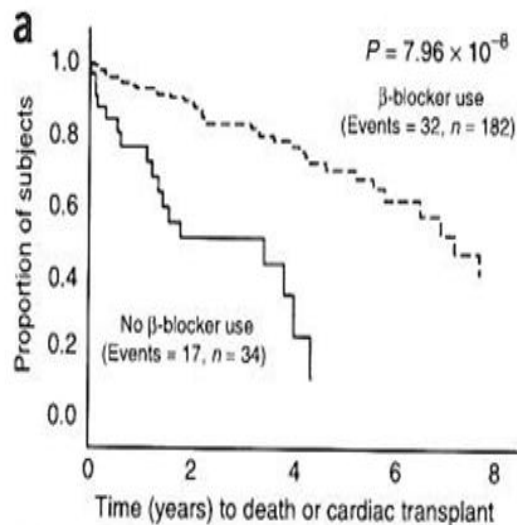
Charles Rotimi - [crggh.nih.gov](http://crggh.nih.gov)



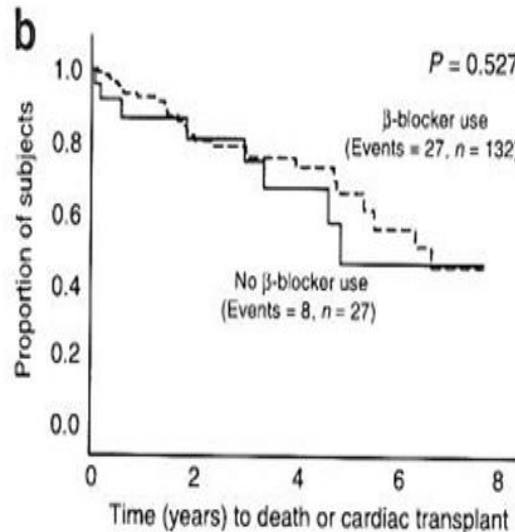
# A GRK5 polymorphism that inhibits $\beta$ -adrenergic receptor signaling is protective in heart failure

1. G protein-coupled receptor kinases (GRKs) desensitize  $\beta$ -adrenergic receptors ( $\beta$ ARs).
2. Re-sequencing of GRK5 revealed a nonsynonymous polymorphism - leucine is substituted for glutamine at position 41; GRK5-Leu41 allele is common in AA (~40%).
3. Results offer an explanation for the confusion in the findings of clinical trials of  $\beta$ -blocker.  **$\beta$ -blockers are absolutely effective in AA without the variant.**

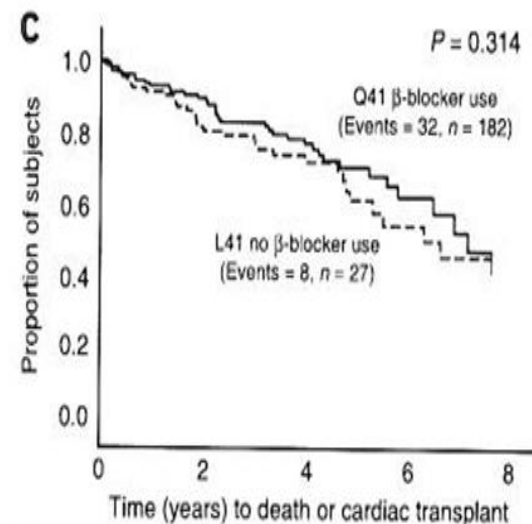
GRK5-Q41 only - with and without  $\beta$ -blocker use



GRK5-L41 only - with and without  $\beta$ -blocker use



GRK5-Q41 only txt with  $\beta$ -blocker vs GRK5-L41 only



# APOL1 and Kidney Disease

**OR=10.5 for ESRD for carriers of two copies of the APOL1 risk allele**

Freq of APOL1 risk variant SNP rs73885319 varies worldwide:

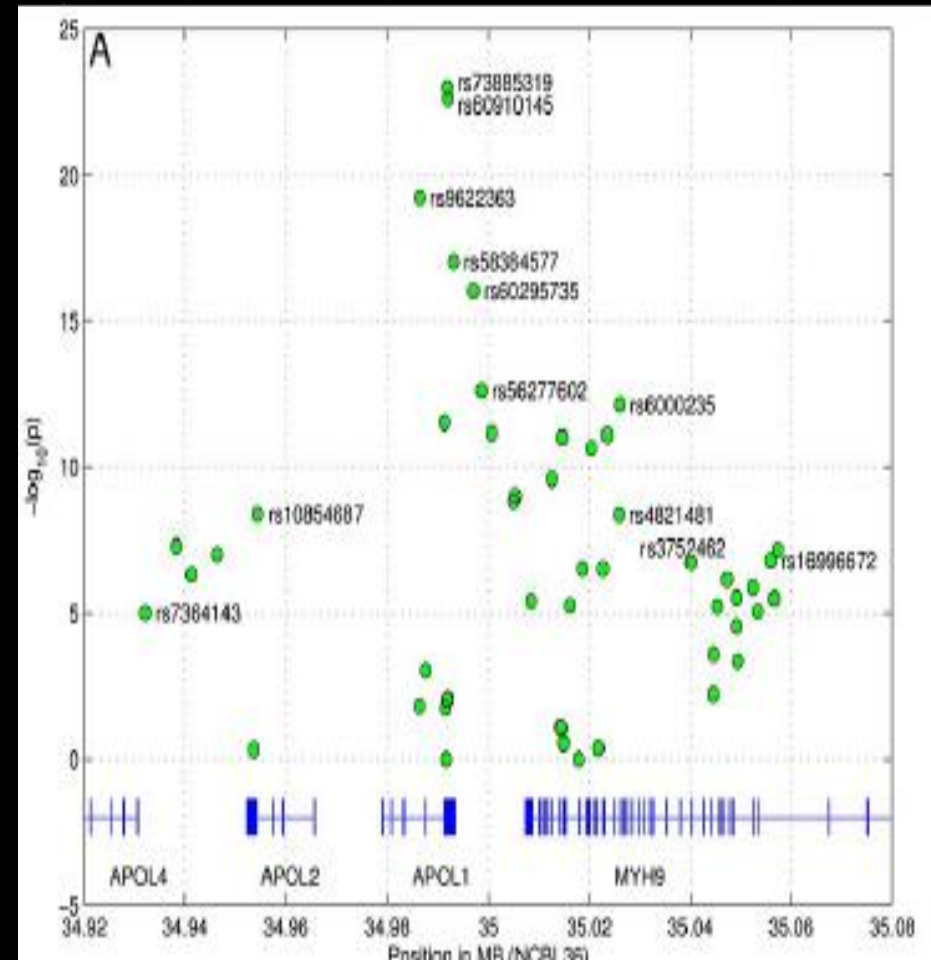
Yoruba - 0.4

African American - 0.2

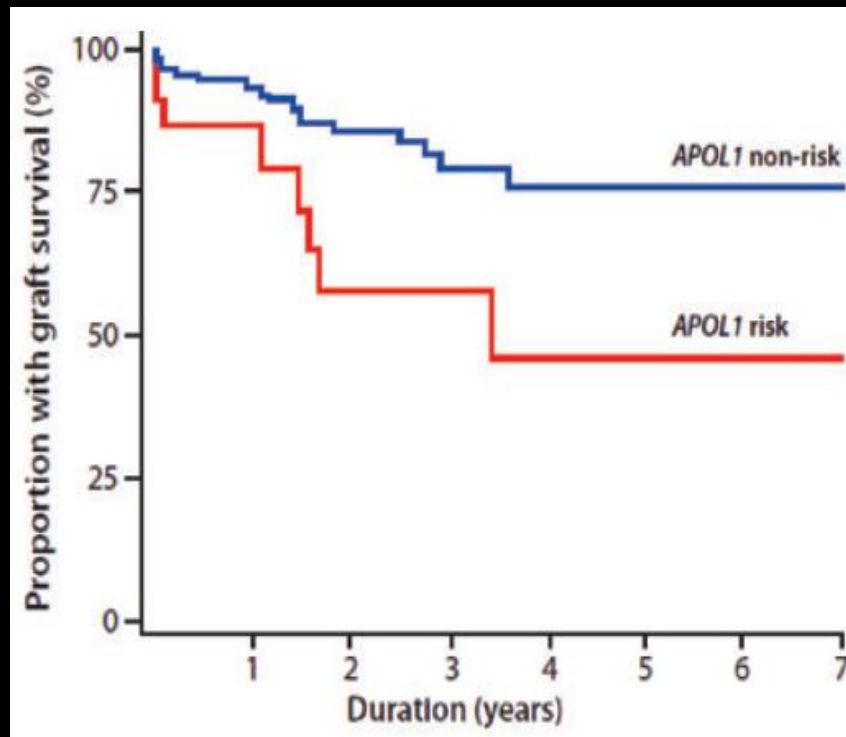
Absent in Europeans and Asians

APOL 1 is a serum factor that lyses trypanosomes. In vitro assays revealed that only the kidney disease-associated ApoL1 variants lysed *Trypanosoma brucei rhodesiense*.

**Kidney disease risk variants likely rose to high freq in Africa because they confer resistance to trypanosomal infection and protect against the lethal form of African sleeping sickness**



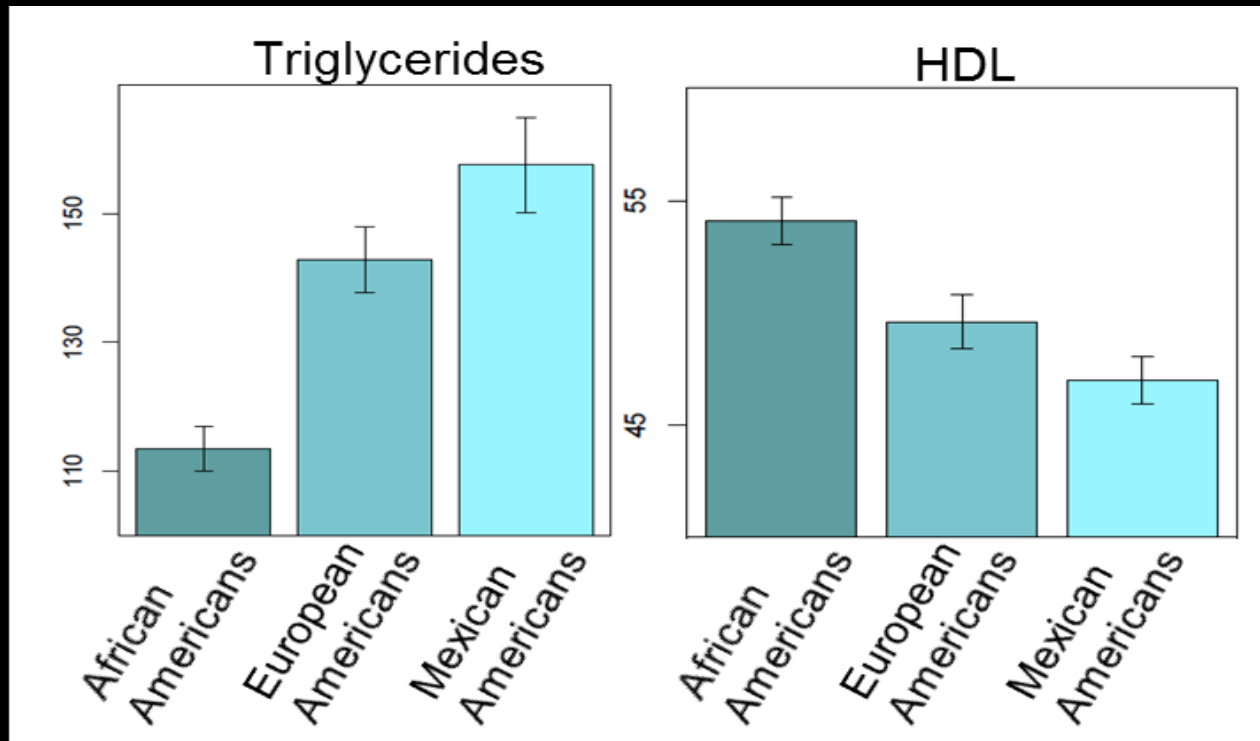
# The *APOL1* Gene and Allograft Survival after Kidney Transplantation



- 136 African American donor kidneys
  - 22 with *APOL1* risk alleles
- Graft survival shorter in donor kidneys with 2 *APOL1* risk variants
  - (HR 3.8,  $p=0.008$ )
- No difference by overall African ancestry

*Graft survival rates from African Americans without the *APOL1* risk alleles were not different than those from non-African American donors.*

# Healthier lipid profile is observed in African ancestry populations - Why?

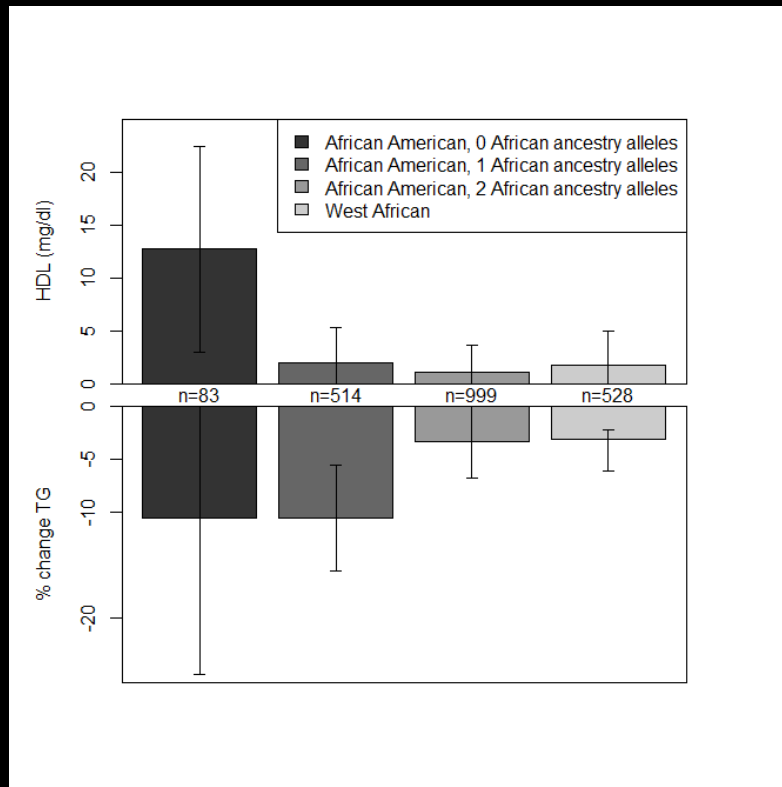


NHANES data: Chang MH, *Circ Cardiovasc Genet*, 2011

# Lipid-Influencing Variants with Ethnicity-Specific Effects in African Americans

## Findings

1. SNP rs328 (*LPL*) associated with higher HDLC and lower TG. Stronger effect was observed on a “European” vs. “African” genetic background.
2. To investigate this ancestry effect, we evaluated the region among West Africans



Individuals cannot be treated as representative for all those who physically resemble them, or have some of the same ancestry.



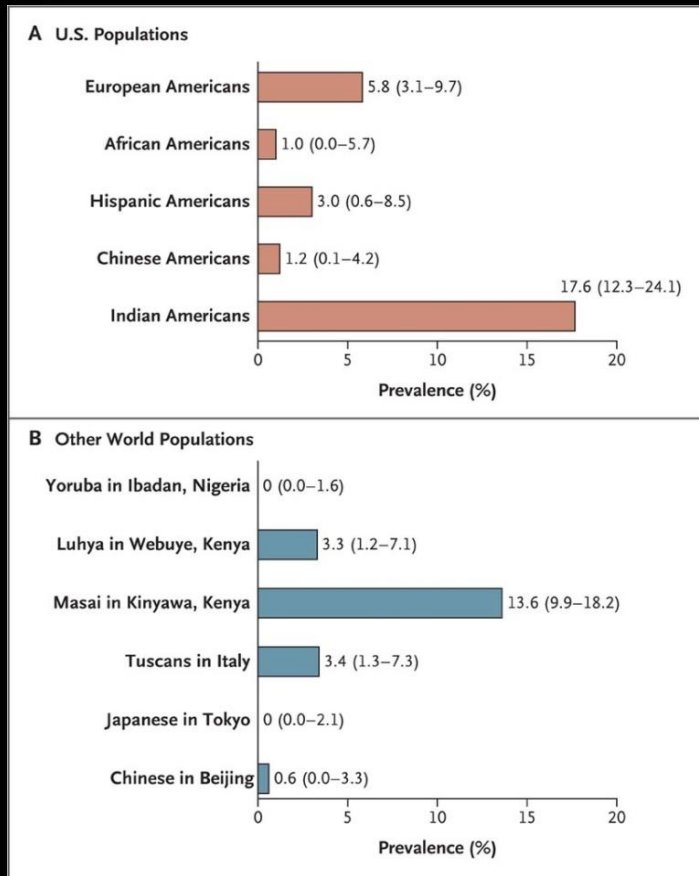
Who is Black?





# The Danger of Group Labelling of Human Genetic Variation

## Genetic Screening to Prevent Abacavir Hypersensitivity (AHS) Reaction



- HLA-B\*5701 - negative predictive value of 100% for patch-test-confirmed AHS for both Whites and Blacks
- Africa - 13.6% (Masai), 0% (Yoruba).
- African Americans – 1%
- Europe – 3.4% (Tuscans), 5.8% (Utah).
- Use of the label “Black” distorts radically different frequency distribution that may lead to wrong public health decision about who to screen.

Variation in the HLA-B\*5701  
Locus in 11 HapMap Samples

Rotimi CN, Jorde LB. **Ancestry and Disease  
in the Age of Genomic Medicine.** (2010)

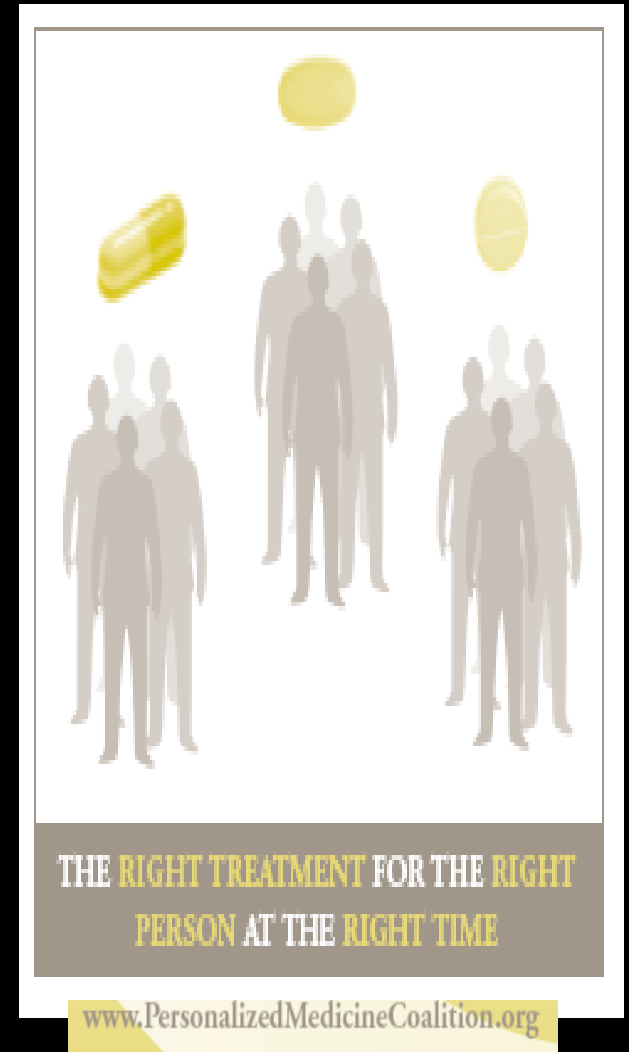


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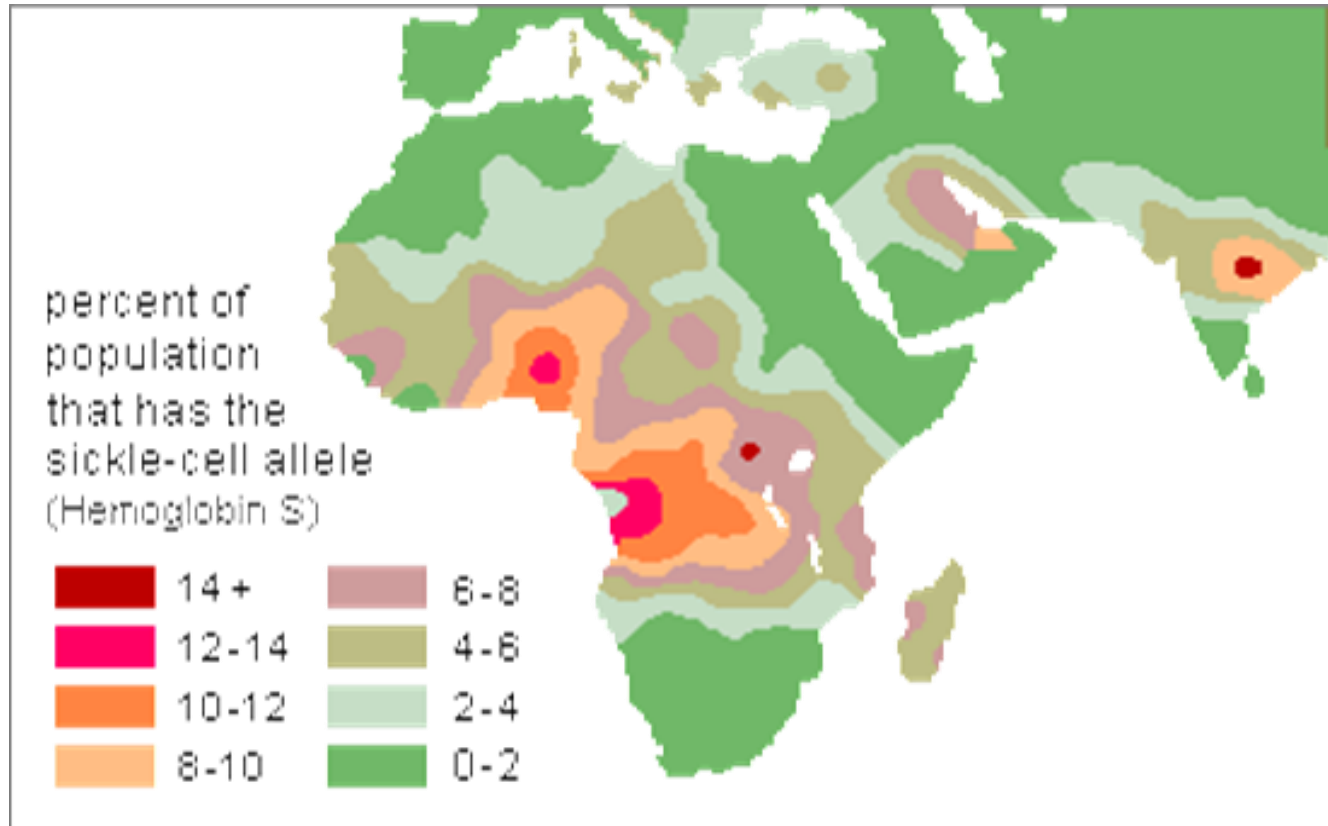
# Precision Medicine

Race and ethnicity are imprecise indicators of who will or will not respond to a drug or have a particular trait/disease

Group definition should be based on individual genotype.



# Regions Affected the most by Sickle Cell Disease



Africa and South Asia have some of the highest rates of sickle cell in the world.



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Thanks

Glad to take Questions

