



# Advances in Health Disparities Genetic Research

- **Charles N. Rotimi, PhD**
- **Director:** Center for Research on Genomics and Global Health
- **Senior Investigator:** Inherited Disease Research Branch



<http://crggh.nih.gov>

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**The central mission of the CRGHH, a trans-NIH center, is to advance research into the role of culture, lifestyle and genomics in disease etiology, differential susceptibilities to disease and variable drug response at the individual and population levels.**



[The Mission](#)  
[Meet The Director](#)  
[The Staff](#)  
[Working Group](#)



<http://crggh.nih.gov>

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## Rationale for Research Activities

To participate in the documentation, description and understanding of the non-random pattern of human genetic variation and its link to disease risks in different Human populations



# Center for Research on Genomics and Global Health

## Research Sites

Africa:

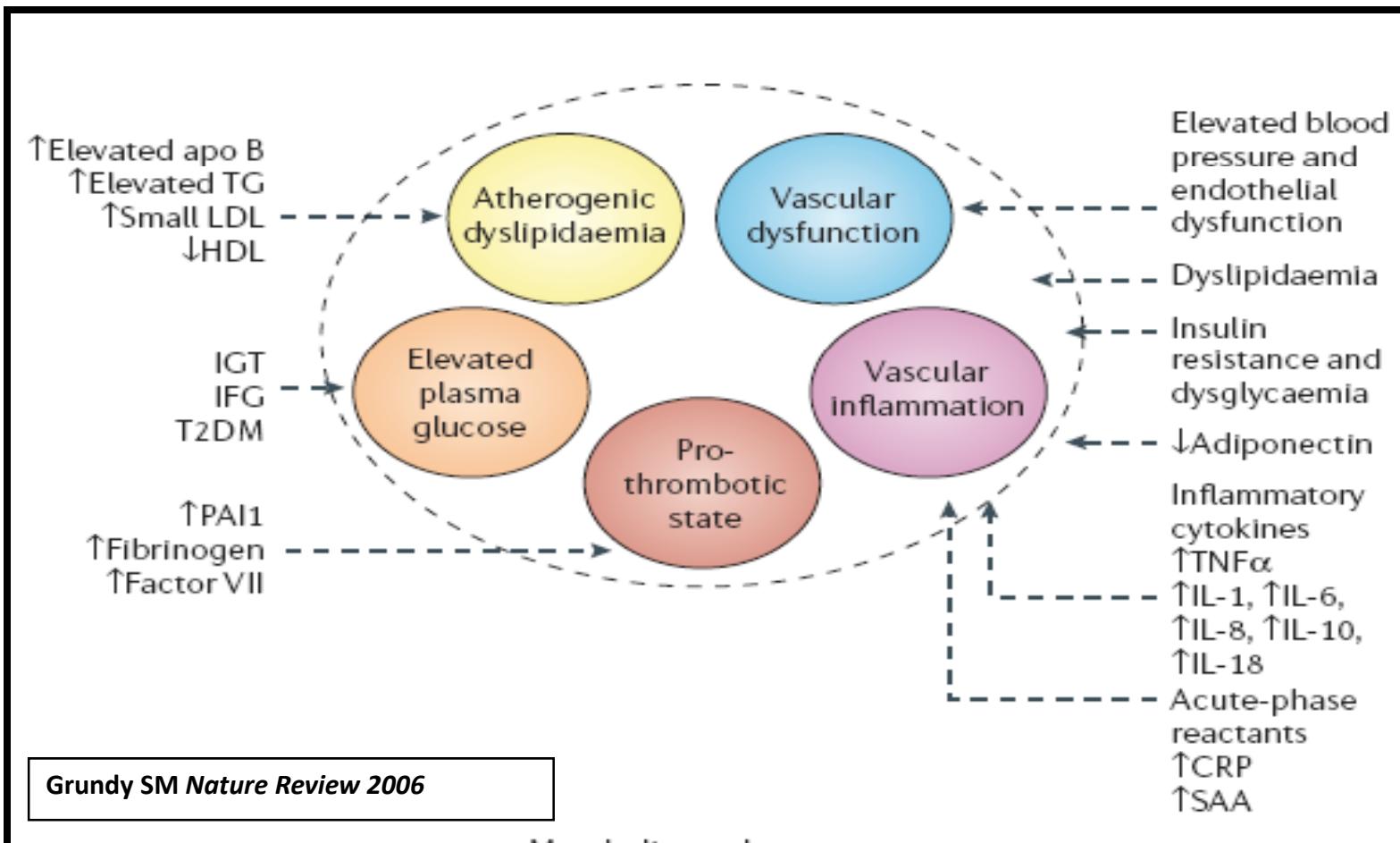
- 1) Nigeria
- 2) Ghana
- 3) Kenya
- 4) Ethiopia

China:  
Suizhou

US:

- 1) Washington, DC  
(African Americans)
- 2) Houston, Texas  
(Mexican Americans)

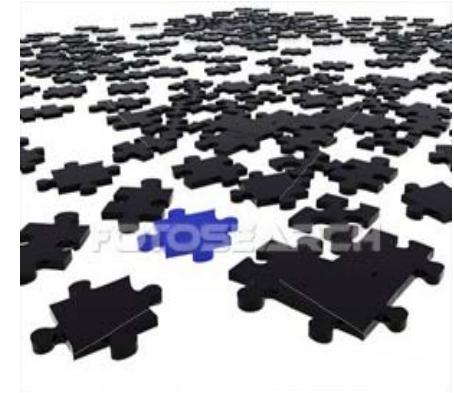
# Clustering of Metabolic Disorders



Patho-biology of the clustering of metabolic disorders including obesity, insulin resistance, hypertension, diabetes, dyslipidemia and chronic kidney disease

# Genomics and Population Differences in Disease Distribution (Health Disparities)

Genomics (genes) - one piece of the puzzle.



k0211562 www.fotosearch.com

- **Concern** – overemphasis on genetic contributors to health disparity may result in neglect of other more important factors including
  - Social, Political and Economic Structure
  - Lifestyle (cultural practices)
  - Environmental exposures

## How the mass incarceration of black men hurts black women

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Between the ages of 20 and 29, one black man in 9 is behind bars. For black women of the same age, the figure is about one in 150

Removing so many men from the marriage market has profound consequences. As incarceration rates exploded between 1970 and 2007, the proportion of US-born black women aged 30-44 who were married plunged from 62 to 33%

70% of black babies are born out of wedlock. Collapse of traditional family has made black Americans far poorer and lonelier than expected.

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# Impact of Social Policy on Health Disparities

Incarceration rates comparing  
Blacks & Whites

Year	Ratio
1933	2.5:1
1950	4.0:1
1960	5.0:1
1970	6.0:1
1989	7.0:1
1995	8.0:1

Ossorio P & Duster T.  
American Psychologist 2005 (115- 128)

## Genomics and Health Disparity

In the words of Charles Darwin,  
quoted on the title page of *The Mismeasure of Man* –

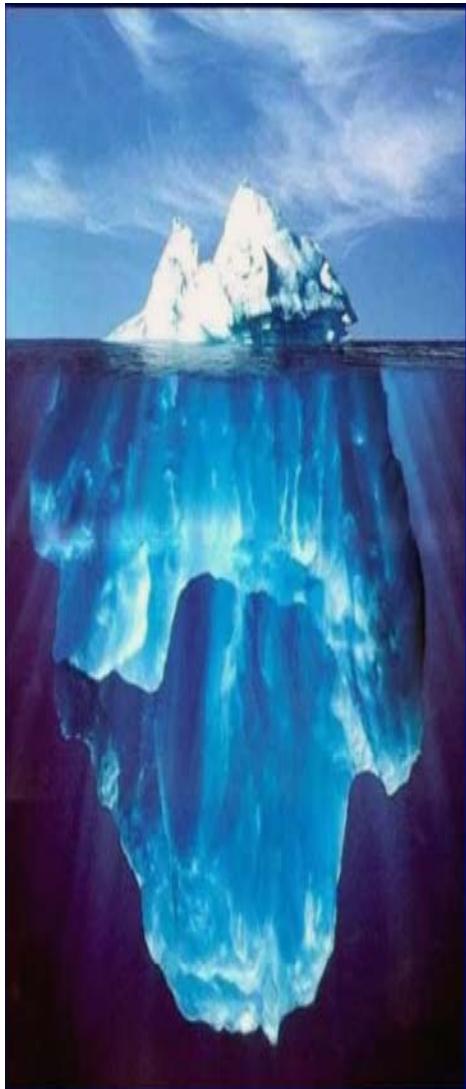
*“If the misery of our poor be caused not by the laws of nature, but by our institutions, great is our sin.”*

# **Genomic Science**

**Enabling Fundamental Insight into biology  
and Human History**

**Medical and Public Health Applications  
are in their infancy but growing**

# Genomic Science - What we are Learning.

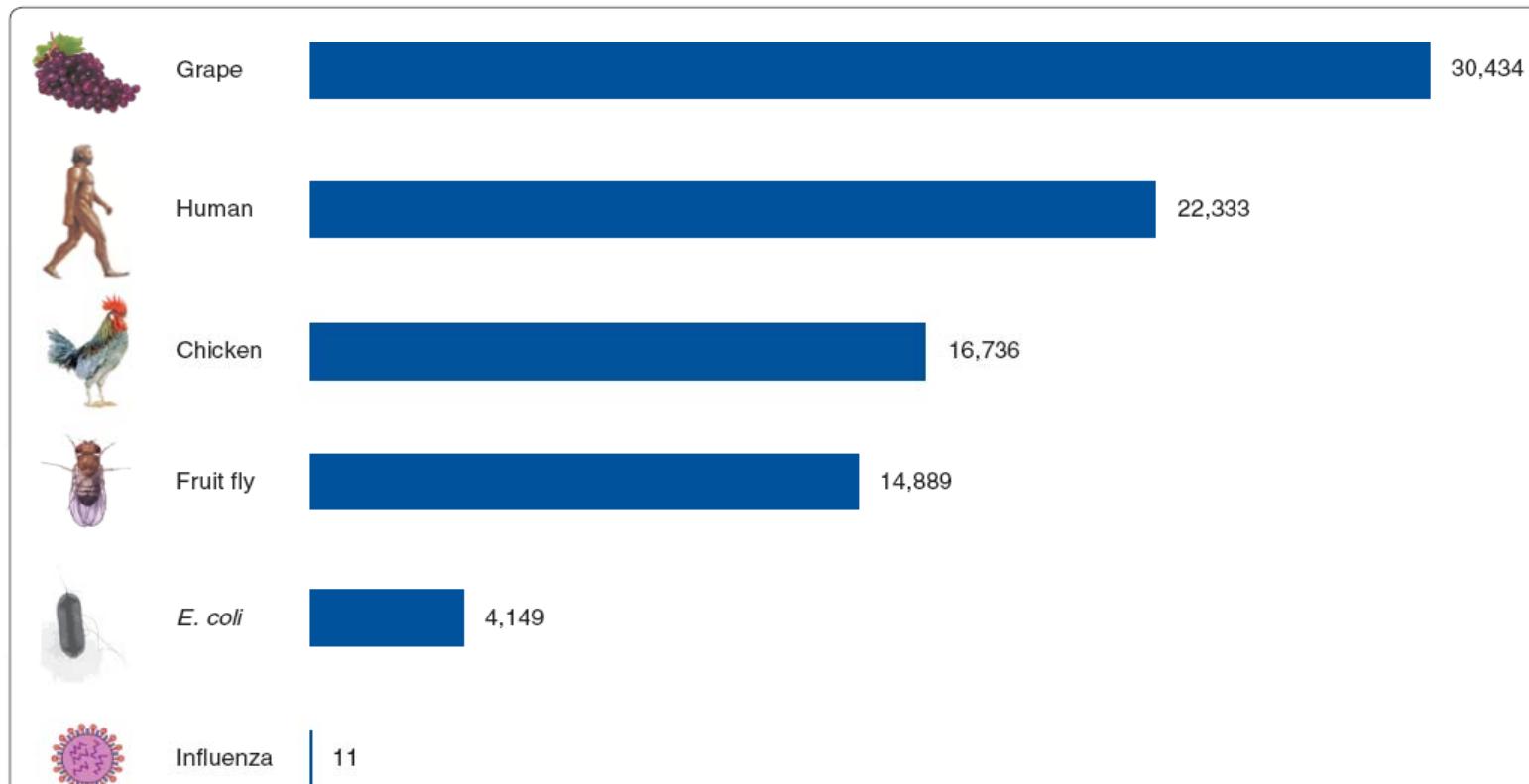


1. Much of the genome is transcribed not just previously annotated genes
2. The expression of intergenic transcripts is subject to the same functional constraints as that of classical exons.
3. Evidence from tiling arrays, which measure transcription without regard to existing annotation, indicates that much of intergenic DNA ("JUNK DNA") is also transcribed.
4. Questions: A) Noise? B) Unidentified RNA gene?  
C) The unannotated exons of existing genes?

*Goymer P. Nature Review October 2006*

# Between a chicken and a grape: estimating the number of human genes

Mihaela Pertea and Steven L Salzberg\*



**Figure 1. Gene counts in a variety of species.** Viruses, the simplest living entities, have only a handful of genes but are exquisitely well adapted to their environments. Bacteria such as *Escherichia coli* have a few thousand genes, and multicellular plants and animals have two to ten times more. Beyond these simple divisions, the number of genes in a species bears little relation to its size or to intuitive measures of complexity. The chicken and grape gene counts shown here are based on draft genomes [50,51] and may be revised substantially in the future.

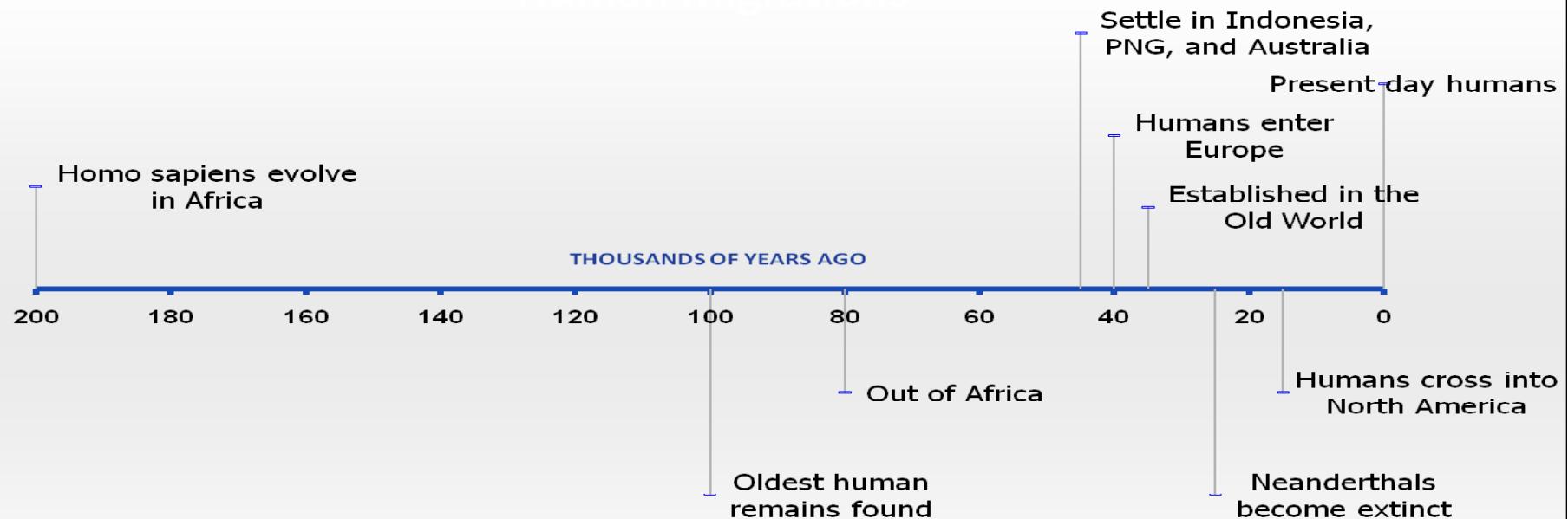
# The Seductive Allure of Behavioral Epigenetics



Different upbringings. Being raised by a nurturing (*top left*) or a lackadaisical (*top right*) mother can cause epigenetic differences that affect a rat pup's behavior later in life. Whether similar differences occur in people raised in wealthy (*bottom left*) or impoverished (*bottom right*) neighborhoods remains an open question.

# What is the genome teaching us about human history?

#### Brief Timeline of Modern Humans



## the Neandertal Genome

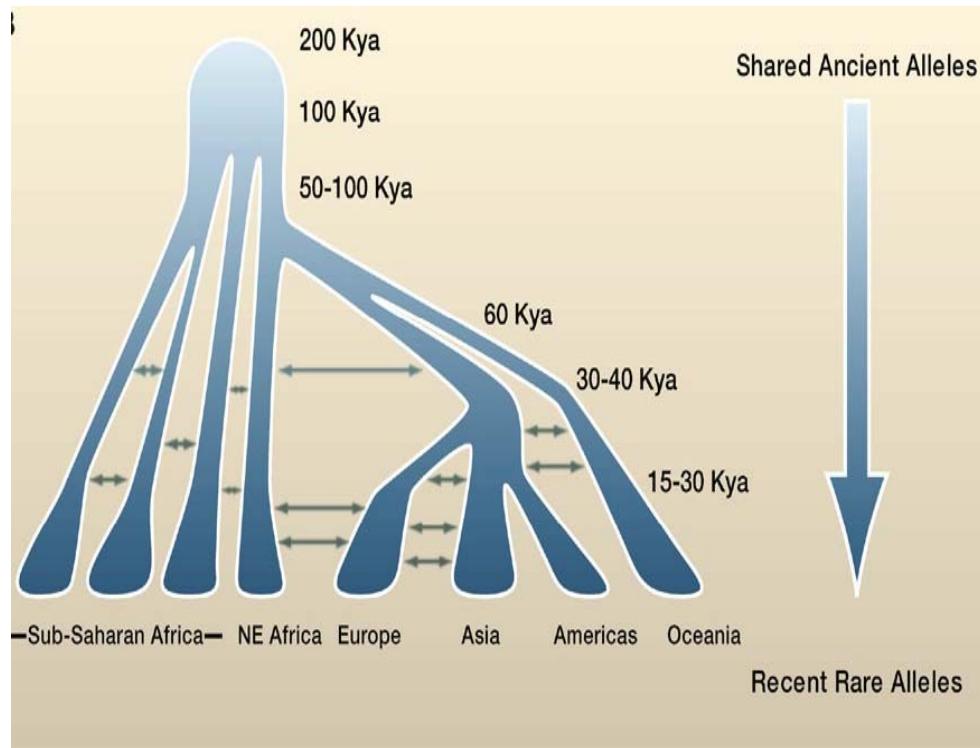


Neandertal ancestry in out-of-Africa human populations.  
No traces of Neandertal heritage in the two African people studied – likely that interbreeding between Neandertals and humans took place in the Middle East as humans began migrating out of Africa to colonize the rest of the world.

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# Human Migrations and Genetic Diversity

## Origins of common and rare alleles



The oldest human alleles originated in Africa well before the diasporas of modern humans.

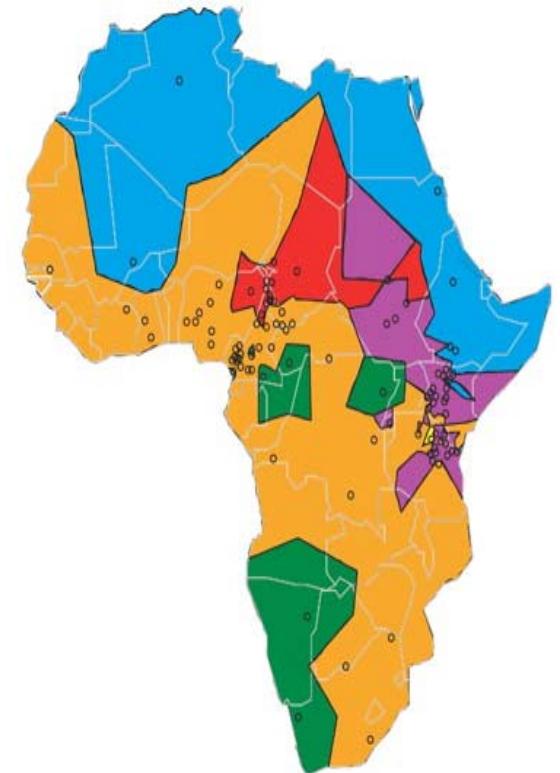
These oldest alleles are common in all populations worldwide. Approximately 90% of the variability in allele frequencies is of this sort.

Development of agriculture in the past 10,000 years and of urbanization and industrialization in the past 700 years led to rapid populations growth and the appearance of vast numbers of new alleles, each individually rare and specific to one population or even to one family.

# The Genetic Structure and History of Africans and African Americans

Sarah A. Tishkoff,<sup>1,2\*</sup> Floyd A. Reed,<sup>1†‡</sup> Françoise R. Friedlaender,<sup>3‡</sup> Christopher Ehret,<sup>4</sup>

- Language, Geographic and Genetic diversity - Distinguishes 6 clusters.
- “Orange” extends from west, through central, to south Africa – Niger-Kordofanian
- “Green” – noncontiguous geographic - pygmy and southern African Khoesan
- “Blue” - Afroasiatic (and Dogon) speaking populations – N. Africa, Mali, Ethiopia, N. Kenya
- Chadic-speaking and Nilo-Saharan speaking make up “red”.
- “Purple” - Cushitic , Nilo-Saharan and some Bantu – Sudan, Kenya, Tanzania, Rwanda - **evidence of gene flow ~ past 5000 year**
- Hadza stand alone (“yellow”).



SCIENCE VOL 324 22 MAY 2009

**Conclusion – High level of mixed ancestry in most populations – reflecting historic migration across the continent**

# Phenotypic Variation Across the Continent From Skin Color, Hair texture, head shape and others

Adioukrou,  
Ivory Coast



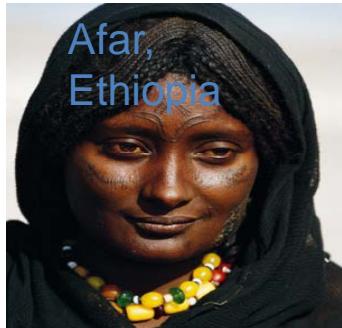
Dogon,  
Mali



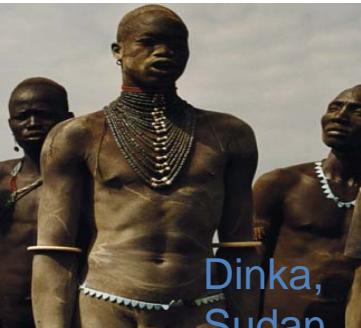
Fulani,  
Mali



Afar,  
Ethiopia



Dinka,  
Sudan



Hausa,  
Nigeria



Wodaabe,  
Niger



Masai,  
Kenya



Surma,  
Ethiopia



Pokot,  
Kenya



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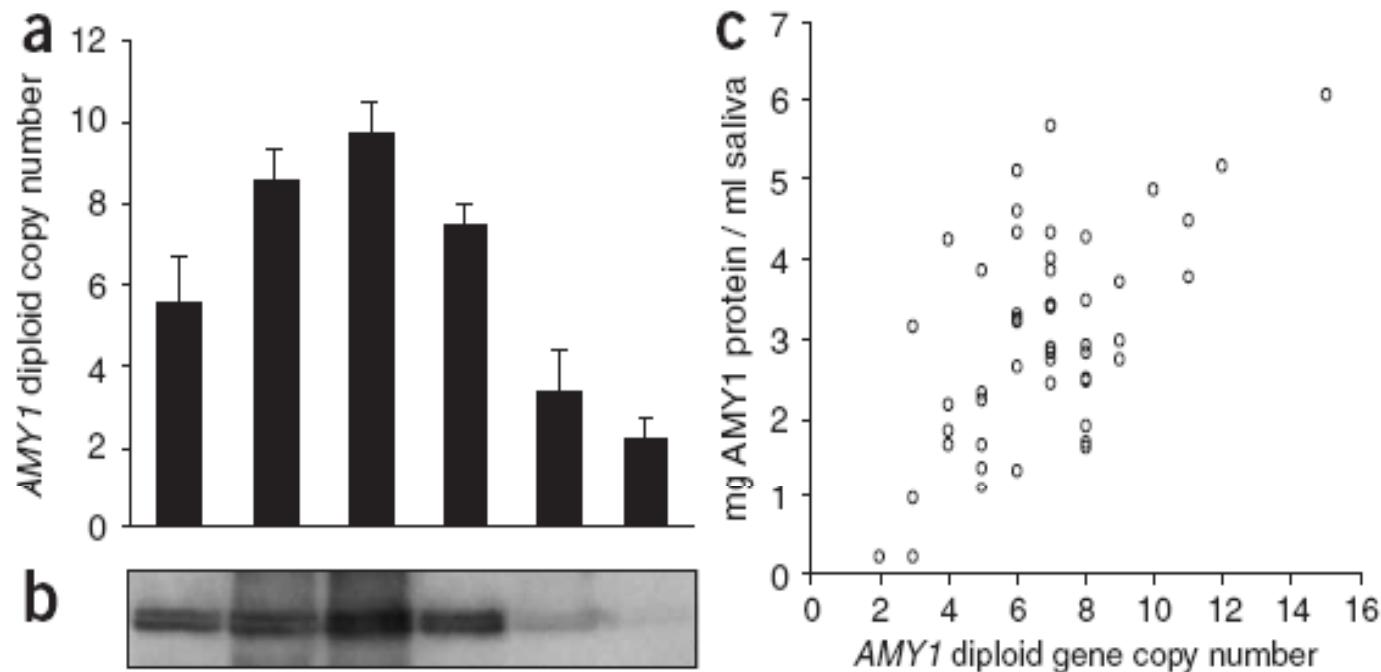
# **Genome-wide detection and characterization of positive selection in human populations**

Pardis C. Sabeti<sup>1\*</sup>, Patrick Varilly<sup>1\*</sup>, Ben Fry<sup>1</sup>, Jason Lohmueller<sup>1</sup>, Elizabeth Hostetter<sup>1</sup>, Chris Cotsapas<sup>1,2</sup>, Xiaohui Xie<sup>1</sup>, Elizabeth H. Byrne<sup>1</sup>, Steven A. McCarroll<sup>1,2</sup>, Rachelle Gaudet<sup>3</sup>, Stephen F. Schaffner<sup>1</sup>, Eric S. Lander<sup>1,4,5,6</sup>  
& The International HapMap Consortium†

Population	Gene	Selection Pressure
Ibadan, Nigeria	LARGE, DMD	Infection – Lassa virus
Utah, USA	SCL24A5, SLC45A2	Skin Pigmentation in Europe
China/Japan	EDAR & EDA2R (Ectodysplasin pathway)	Development of hair follicles in Asia

# Diet and the evolution of human amylase gene copy number variation

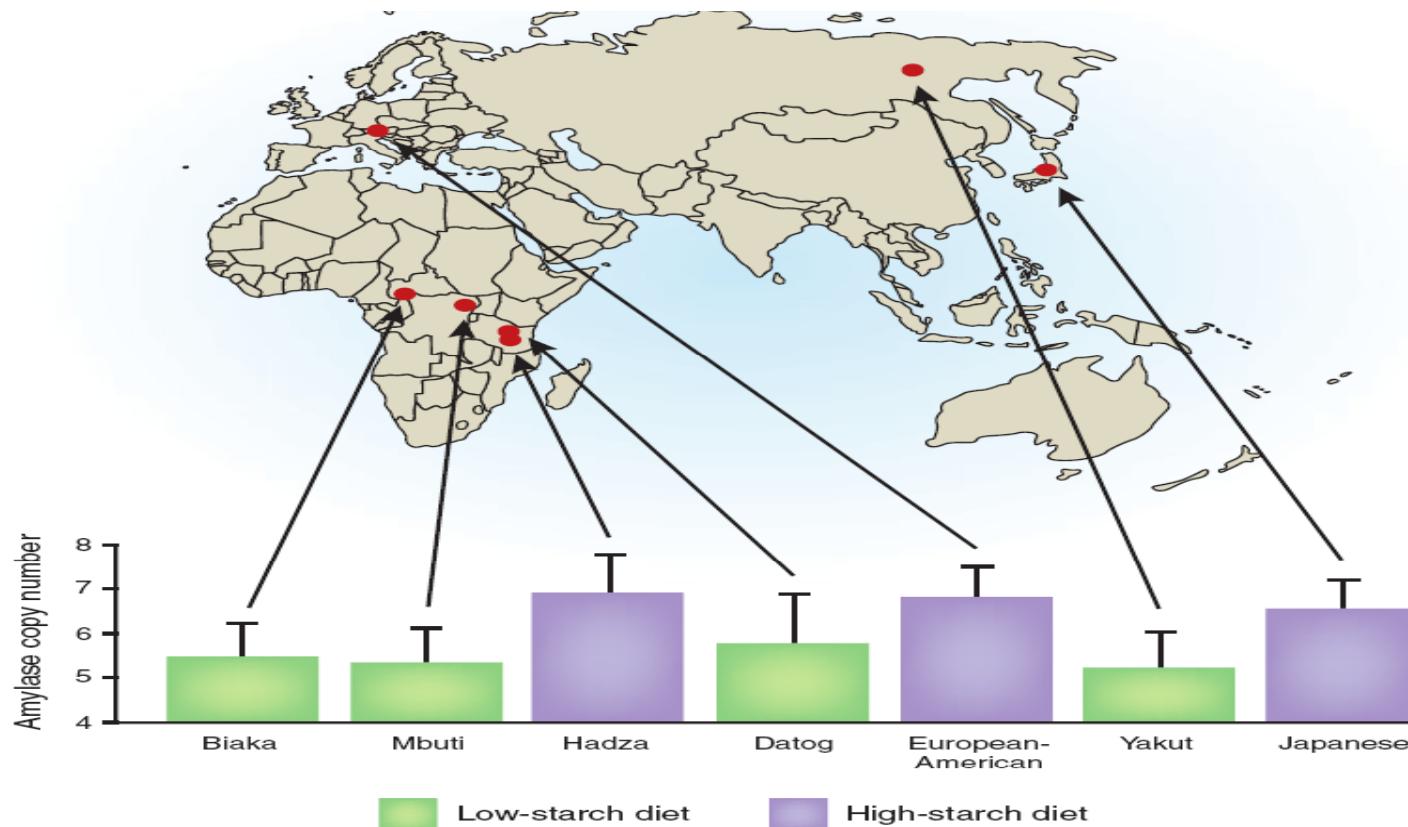
George H Perry<sup>1,2</sup>, Nathaniel J Dominy<sup>3</sup>, Katrina G Claw<sup>1,4</sup>, Arthur S Lee<sup>2</sup>, Heike Fiegler<sup>5</sup>, Richard Redon<sup>5</sup>,



Gene copy number explained 35% of the variability in salivary amylase protein expression – leaving room for other genetic and non-genetic factors including hydration status, stress level and short term dietary habits.

# Adaptive drool in the gene pool

John Novembre, Jonathan K Pritchard & Graham Coop



**Figure 1** The distribution of salivary amylase copy number in the seven samples from Perry *et al.*<sup>1</sup>. The bar chart depicts the mean copy number per sample, with an interval of two standard errors above the mean. Mean copy number is found to be higher in populations with high-starch diets, even when samples are relatively near one another geographically (for example, comparing Hadza and Datog or Yakut and Japanese populations).

Charles Rotimi — crrgh.nih.gov

VOLUME 39 | NUMBER 10 | OCTOBER 2007 | NATURE GENETICS

# Complete Khoisan and Bantu genomes from southern Africa

Stephan C. Schuster<sup>1\*</sup>, Webb Miller<sup>1\*</sup>, Aakrosh Ratan<sup>1</sup>, Lynn P. Tomsho<sup>1</sup>, Belinda Giardine<sup>1</sup>, Lindsay R. Kasson<sup>1</sup>,



"On average, there are more genetic differences between any two Bushmen in our study than between a European and an Asian"

The study identified 1.3-million genetic variants that scientists previously had not observed. These genetic variations reveal that Southern Africans are quite distinct genetically from Europeans, Asians, and West Africans.

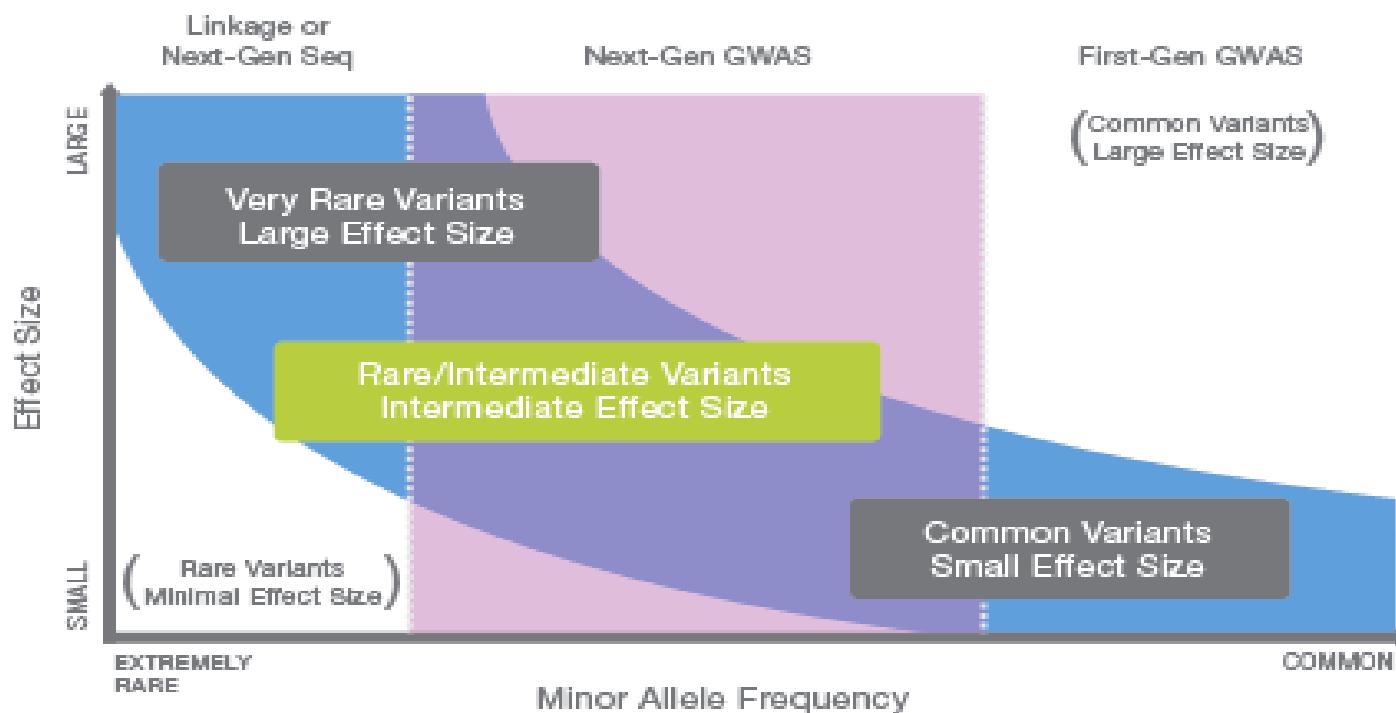
# Using Genomic Tools to Understand Disease etiology and disparities

Charles Rotimi - crggh.nih.gov

# Genome-Wide Association Studies - GWAS

The fundamental premise behind these GWAS was that common diseases, such as diabetes or high blood pressure, were caused by common genetic variants, alleles that have high frequencies within the afflicted population (generally > 5% minor allele frequency, or MAF).

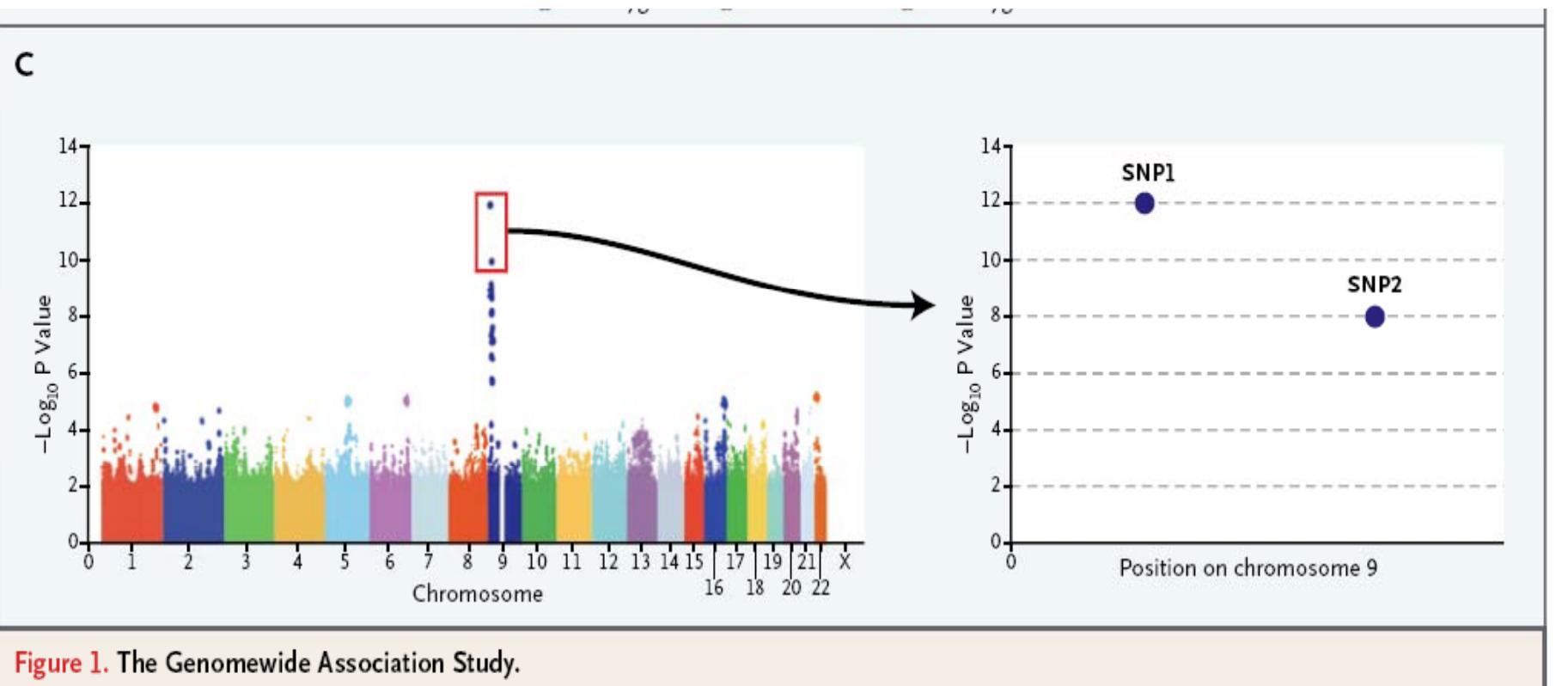
**Figure 1: The Spectrum of Genetic Variation**



[http://www.illumina.com/documents/icommunity/article\\_2010\\_06\\_next-gen\\_gwas.pdf](http://www.illumina.com/documents/icommunity/article_2010_06_next-gen_gwas.pdf)

# Genomewide Association Studies and Assessment of the Risk of Disease

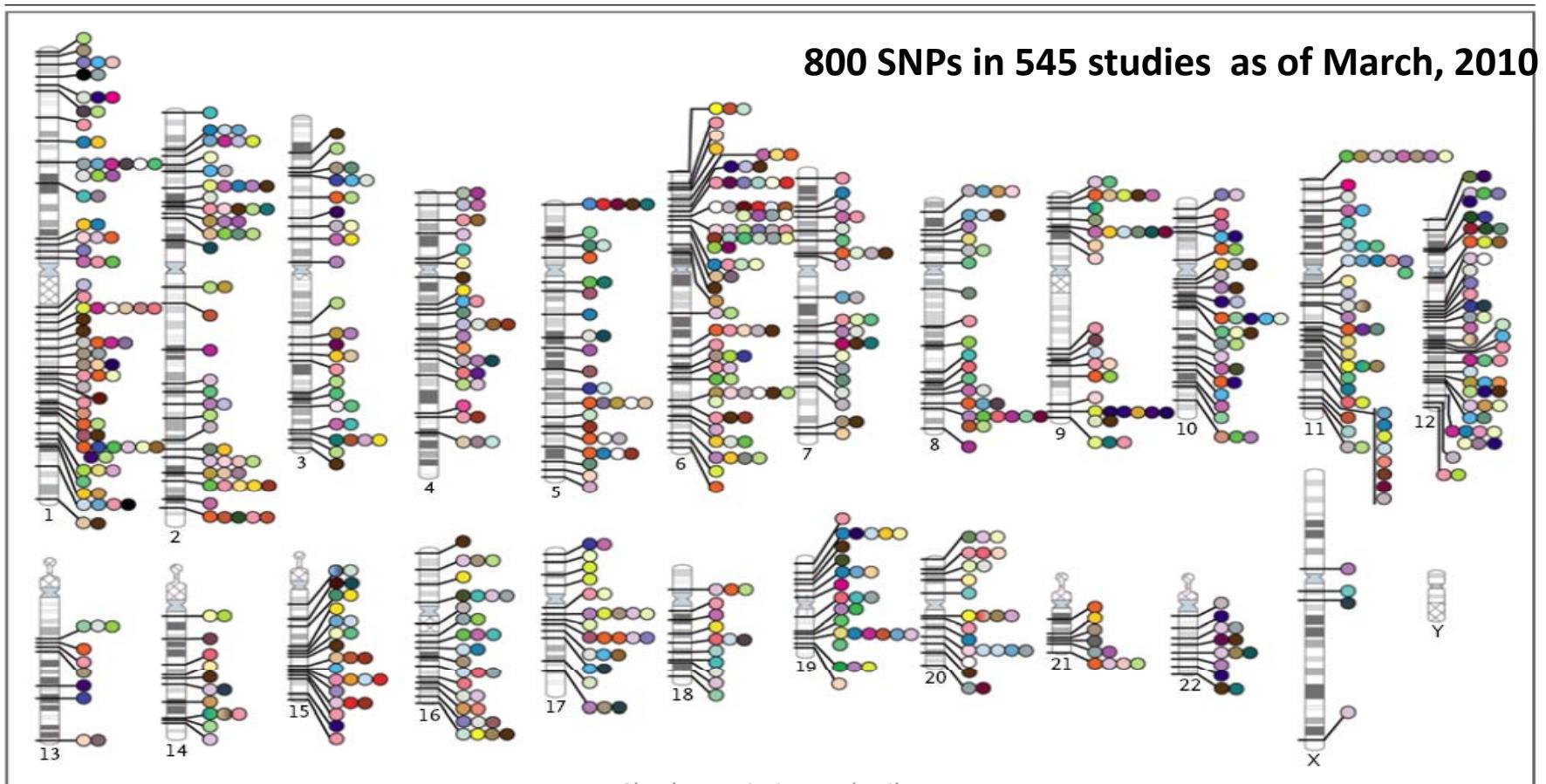
Teri A. Manolio, M.D., Ph.D.



The NEW ENGLAND JOURNAL of MEDICINE

# Genomewide Association Studies and Assessment of the Risk of Disease

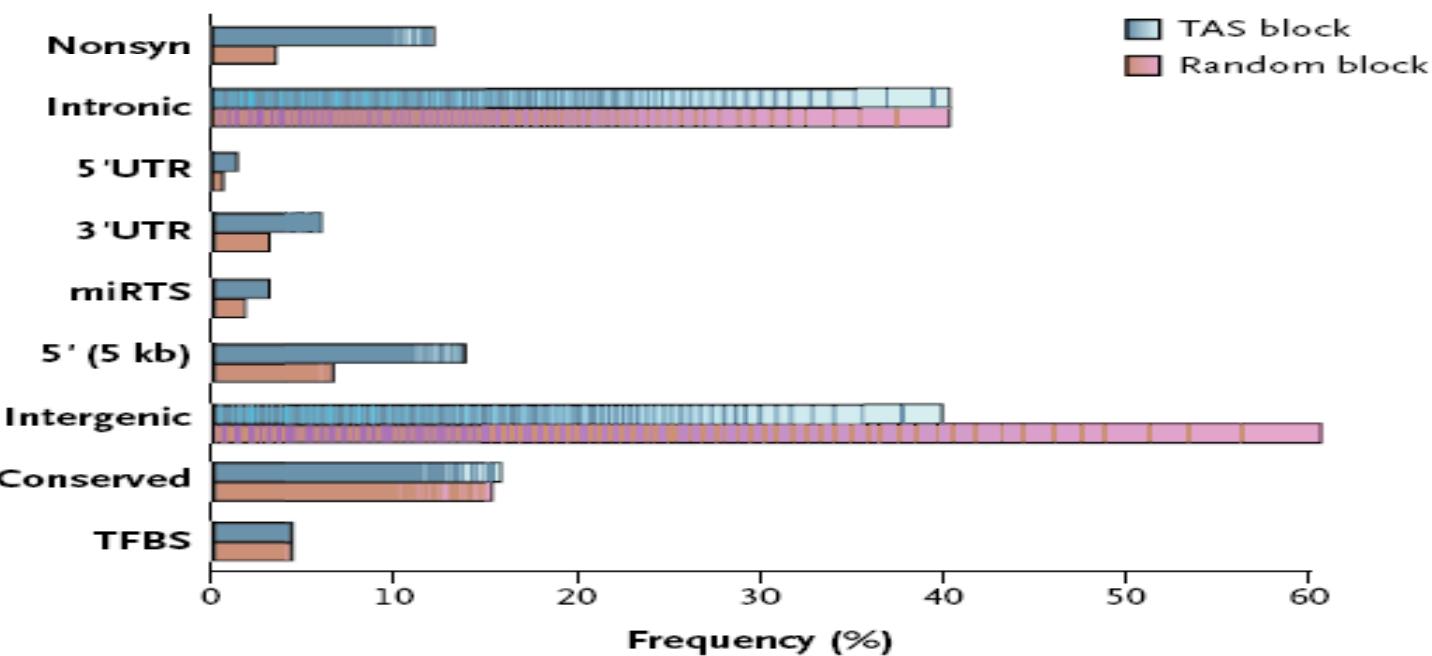
Teri A. Manolio, M.D., Ph.D.



Charles Rotimi - crggh.nih.gov

## Genomewide Association Studies and Assessment of the Risk of Disease

Teri A. Manolio, M.D., Ph.D.



**Figure 4. Functional Classifications of 465 Trait-Associated SNPs and the SNPs in Linkage Disequilibrium with Them.**

1. Only 12% of SNPs associated with traits are located in, or occur in tight linkage disequilibrium with, protein-coding regions of genes
2. Over 80% of trait-associated SNPs are in the intergenic region.

# Genomewide Association Studies and Assessment of the Risk of Disease

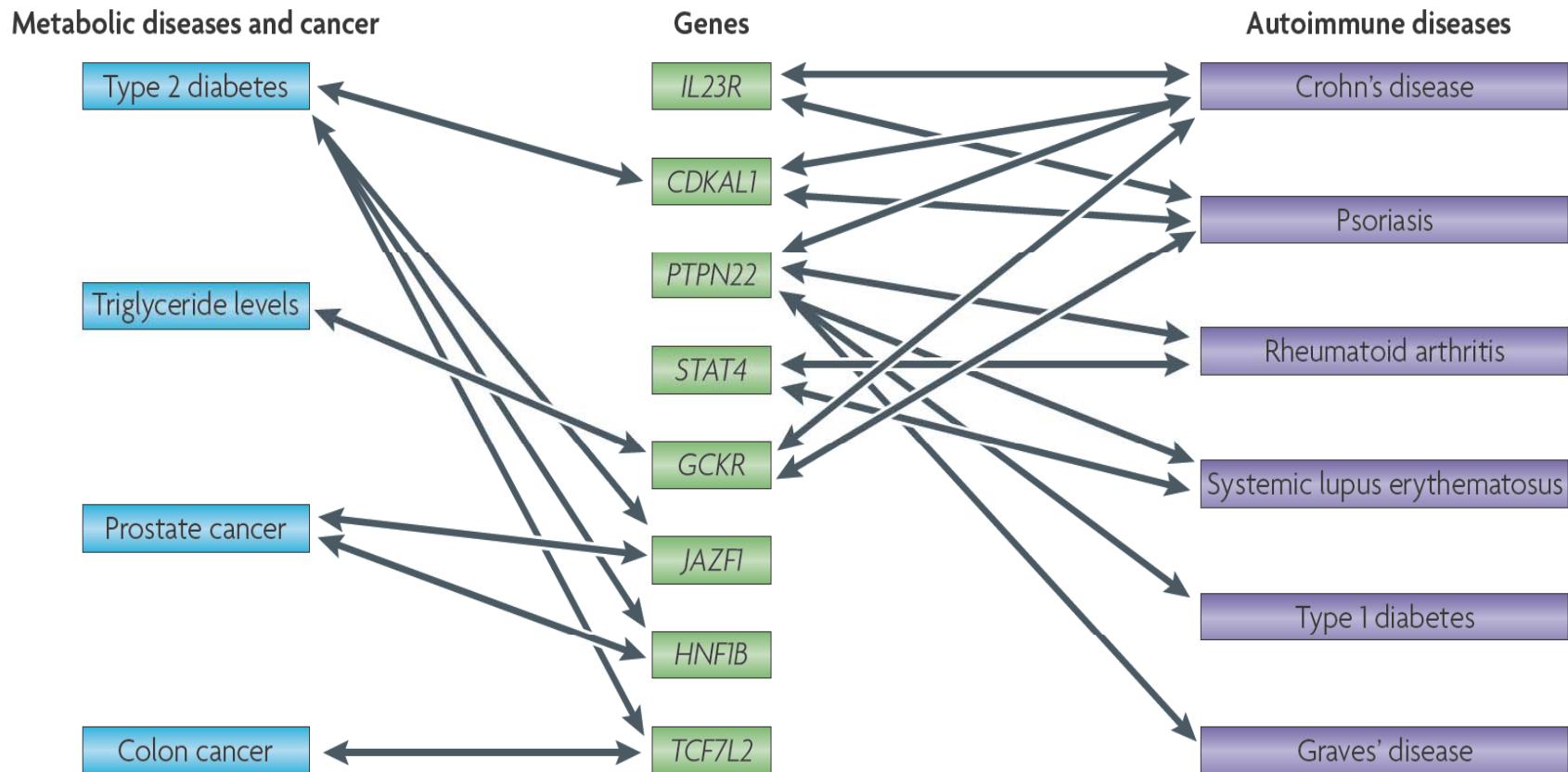
Teri A. Manolio, M.D., Ph.D.

NEJM - March, 2010

**Table 1.** Examples of Previously Unsuspected Associations between Certain Conditions and Genes and the Related Metabolic Function or Pathway, According to Genomewide Association Studies.

Condition	Gene	Function or Pathway	Source of Data
Age-related macular degeneration	CFH	Complement-mediated inflammation	Klein et al. <sup>25</sup>
Coronary disease	CDKN2A, CDKN2B	Cell-cycle regulator	Helgadottir et al. <sup>36</sup>
Childhood asthma	ORMDL3	Unknown	Moffatt et al. <sup>37</sup>
Type 2 diabetes	CDKAL1	Cell-cycle regulator	Scott et al. <sup>3</sup>
Crohn's disease	ATG16L1	Autophagy	Rioux et al. <sup>38</sup>

# Overlap of genetic risk factor loci for common diseases.



Frazer KA et al, Nat Rev Genet. 2009 Apr;10(4):241-51.  
Charles Rotimi - crggh.nih.gov

How is GWAS and other genomic approaches  
informing differential susceptibility to  
disease and variable drug response?

# A second generation human haplotype map of over 3.1 million SNPs

Nature. 2007 Oct 18;449(7164):851-61.

The International HapMap Consortium\*

**Table 3 | Number of tag SNPs required to capture common ( $MAF \geq 0.05$ )**

## Phase II SNPs

Threshold	YRI	CEU	CHB+JPT
$r^2 \geq 0.5$	627,458	290,969	277,831
$r^2 \geq 0.8$	1,093,422	552,853	520,111
$r^2 = 1$	1,616,739	1,024,665	1,078,959

Platform	Yoruba (YRI)	CEU
$r \geq 0.8$ (%)	$r \geq 0.8$ (%)	$r \geq 0.8$ (%)
Affymetrix 500K	46	68
Affy Array 6.0	66	82
Illumina HumanHap550	55	88
Illumina HumanHap650Y	66	89

# Next generation disparities in human genomics: concerns and remedies

Anna C. Need and David B. Goldstein

Table 1. Ethnicity of participants in genome-wide association studies<sup>a</sup>

Race/ethnicity	Number of studies	Total participants <sup>d</sup>	Average sample size
European only <sup>b</sup>	320	1 581 776	4943
Asian only	26	52 841	2032
Hispanic only	3	1019	340
Native American only	2	1102	551
Jewish only	2	3479	1740
Gambian only	1	2340	2340
Micronesian only	1	2346	2346
Mixed <sup>c</sup>	11	European <sup>b,e</sup> African-American Asian Papua-New Guinean Other <sup>f</sup>	European <sup>b</sup> African-American Asian Papua-New Guinean Other <sup>f</sup>
		92 437 7500 33 276 269	8403 682 3 276 <sup>g</sup> 24

# A Genome-Wide Association Study of Hypertension and Blood Pressure in African Americans

**Adebawale Adeyemo<sup>1\*</sup>, Norman Gerry<sup>2</sup>, Guanjie Chen<sup>1</sup>, Alan Herbert<sup>3</sup>, Ayo Doumatey<sup>1</sup>, Hanxia Huang<sup>1</sup>, Jie Zhou<sup>1</sup>, Kerrie Lashley<sup>4</sup>, Yuanxiu Chen<sup>4</sup>, Michael Christman<sup>2</sup>, Charles Rotimi<sup>1\*</sup>**

**1** Center for Research on Genomics and Global Health, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, United States of America, **2** The Coriell Institute for Biomedical Research, Camden, New Jersey, United States of America, **3** Department of Genetics and Genomics, Boston University, Boston, Massachusetts, United States of America, **4** National Human Genome Center, Howard University, Washington, D.C., United States of America

## Abstract

The evidence for the existence of genetic susceptibility variants for the common form of hypertension ("essential hypertension") remains weak and inconsistent. We sought genetic variants underlying blood pressure (BP) by conducting a genome-wide association study (GWAS) among African Americans, a population group in the United States that is disproportionately affected by hypertension and associated complications, including stroke and kidney diseases. Using a dense panel of over 800,000 SNPs in a discovery sample of 1,017 African Americans from the Washington, D.C., metropolitan region, we identified multiple SNPs reaching genome-wide significance for systolic BP in or near the genes: PMS1, SLC24A4, YWHA7, IPO7, and CACNA1H. Two of these genes, SLC24A4 (a sodium/potassium/calcium exchanger) and CACNA1H (a voltage-dependent calcium channel), are potential candidate genes for BP regulation and the latter is a drug target for a class of calcium channel blockers. No variant reached genome wide significance for association with diastolic BP (top scoring SNP rs1867226,  $p = 5.8 \times 10^{-7}$ ) or with hypertension as a binary trait (top scoring SNP rs9791170,  $p = 5.1 \times 10^{-7}$ ). We replicated some of the significant SNPs in a sample of West Africans. Pathway analysis revealed that genes harboring top-scoring variants cluster in pathways and networks of biologic relevance to hypertension and BP regulation. This is the first GWAS for hypertension and BP in an African American population. The findings suggests that, in addition to or in lieu of relying solely on replicated variants of moderate-to-large effect reaching genome-wide significance, pathway and network approaches may be useful in identifying and prioritizing candidate genes/loci for further experiments.

**Table 3.** Top associated SNPs for Systolic BP and Diastolic BP.

Rank	SNP	Chr	Position	Type	Closest gene	Distance to gene (kb)	Allele	MAF	P
<b>Systolic BP</b>									
1	rs5743185	2	190446083	INTRONIC	PMS1	0	T	0.1418	2.09E-11
2	rs16877320	6	16031005	INTERGENIC	AL365265.23	12	G	0.1316	3.42E-09
3	rs11160059	14	91877083	INTRONIC	SLC24A4	0	A	0.1782	1.54E-08
4	rs17365948	8	102026053	INTRONIC	YWHAZ	0	A	0.1125	1.59E-08
5	rs12279202	11	9388666	INTRONIC	IPO7	0	A	0.1231	4.80E-08
6	rs3751664	16	1194370	NON_SYNONYMOUS_CODING	CACNA1H	0	T	0.1093	6.71E-08
7	rs11659639	18	56318592	INTERGENIC	MC4R	127	C	0.09771	2.13E-07
8	rs4613079	16	79201458	INTRONIC	CDYL2	0	T	0.1766	5.06E-07
9	rs13201744	6	6071844	INTERGENIC	F13A1	17	A	0.16	1.12E-06
10	rs2183737	9	70431453	INTERGENIC	PP11-274B18.3	15	T	0.4592	1.21E-06

Despite highlighted limitations – there are examples of how genome science is contributing to understanding of ethnic and population differences in disease distribution and variable drug response.

ORIGINAL ARTICLE

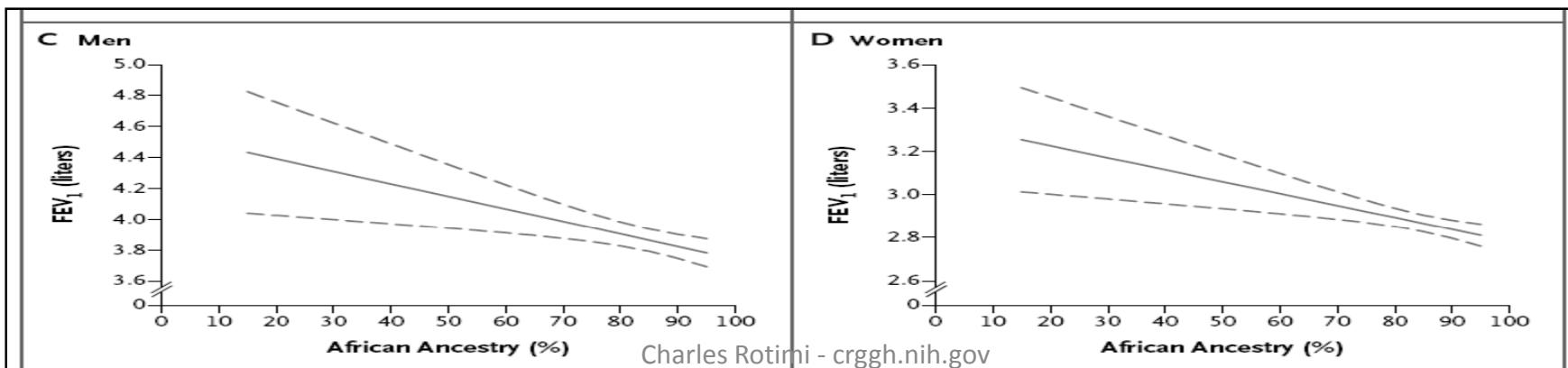
## Genetic Ancestry in Lung-Function Predictions

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

### RESULTS

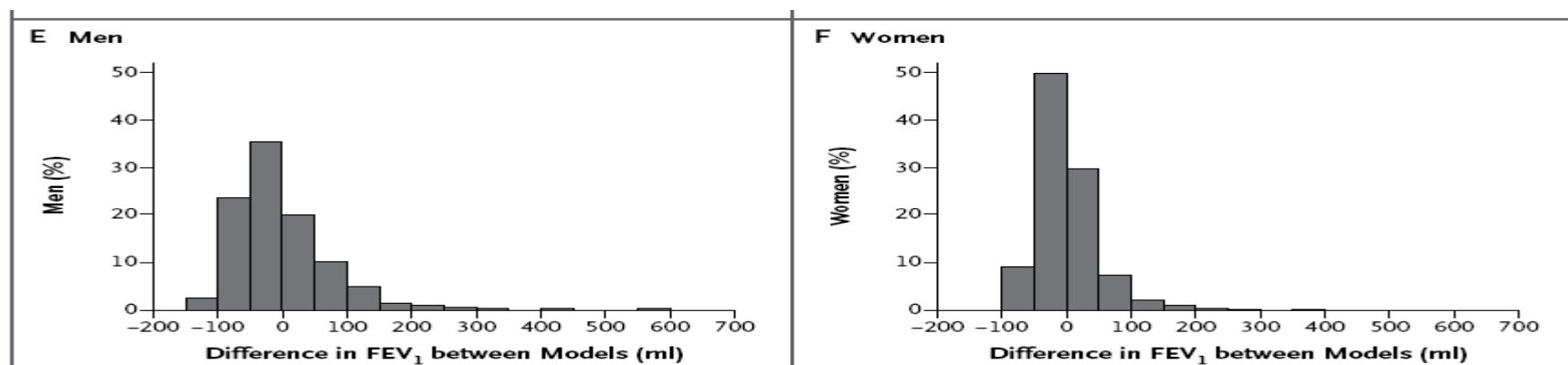
African ancestry was inversely related to forced expiratory volume in 1 second ( $FEV_1$ ) and forced vital capacity in the CARDIA cohort. These relations were also seen in the HABC and CHS cohorts. In predicting lung function, the ancestry-based model fit the data better than standard models. Ancestry-based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

NEJM July 2010



## ORIGINAL ARTICLE

## Genetic Ancestry in Lung-Function Predictions



**Figure 1.** Ancestry, Forced Expiratory Volume in 1 Second (FEV<sub>1</sub>), and Differences in Predicted FEV<sub>1</sub> among CARDIA Study 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.)

Charles Rotimi - crggh.nih.gov

NEJM July 2010

# **Importance of Ancestry in Genomic Studies**

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In this example, frequency of risk variant is different between ancestral populations.

However, the variant is effective in ameliorating the health consequences of Hepatitis C virus infection across all human populations studied to date.

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# 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.

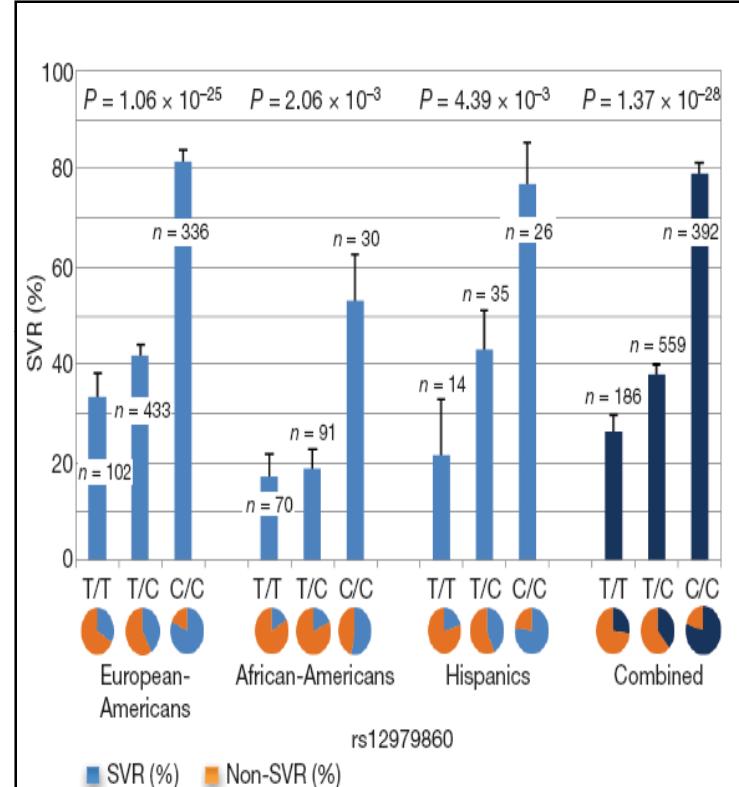


Figure 1 | Percentage of SVR by genotypes of rs12979860. Data are percentages + s.e.m.

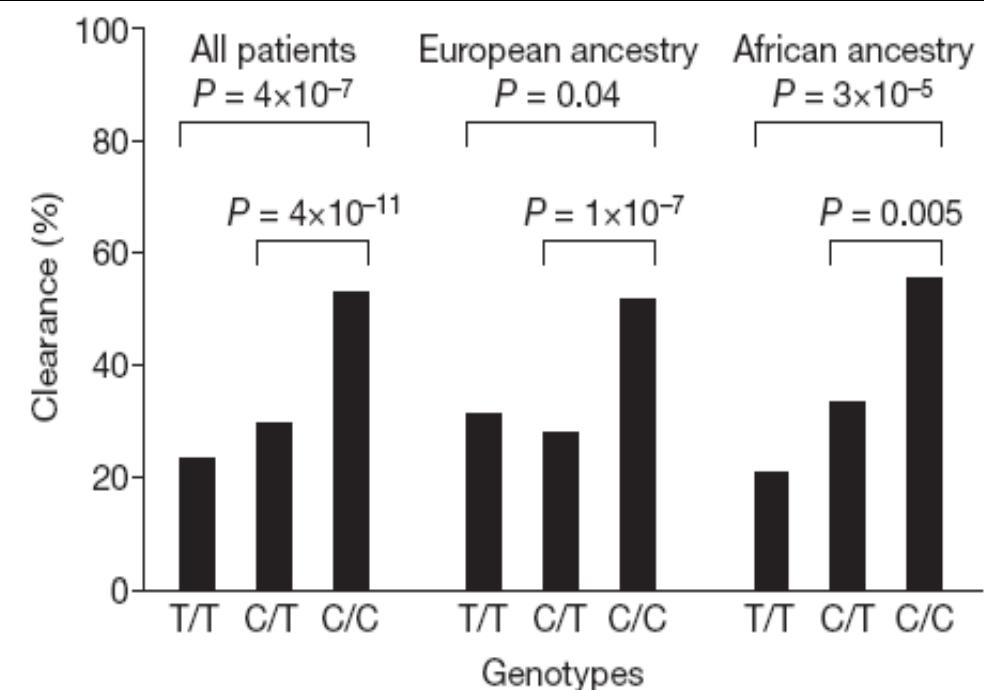
SVR – sustained virological response

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>

Nature – Oct 8, 2009



**Figure 1 | Percentage of HCV clearance by rs12979860 genotype.** Data are shown for all patients, as well as individuals of European ancestry and African ancestry separately.

# **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>

<b>Population Groups</b>	<b># of individuals (# of populations)</b>	<b>Mean Frequency</b>	<b>Frequency Range</b>
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.

# Prostate Cancer

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Prostate cancer (PC) genetics provides compelling, though preliminary, data on the potential role of molecular factors in explaining disparity in diseases between ethnic groups.

8q24 has been associated with PC in men from several ancestral backgrounds including Europeans, Africans, Latinos, and Japanese.

Impact of susceptibility variants in 8q24 varies with ancestry. The PAR for all variants in 8q24 is 32% in European Americans and 68% in African Americans.

**It is important to point out that none of the genetic variants identified in the 8q24 region are in known genes or alter the coding sequence of an encoded protein.**

## ***MYH9* is a major-effect risk gene for focal segmental glomerulosclerosis**

Jeffrey B Kopp<sup>1,17</sup>, Michael W Smith<sup>2,16,17</sup>, George W Nelson<sup>2,17</sup>, Randall C Johnson<sup>2</sup>, Barry I Freedman<sup>3</sup>,

## ***MYH9* is associated with nondiabetic end-stage renal disease in African Americans**

W H Linda Kao<sup>1–3,25</sup>, Michael J Klag<sup>1–3,25</sup>, Lucy A Meoni<sup>2–4</sup>, David Reich<sup>5,6</sup>, Yvette Berthier-Schaad<sup>1</sup>,

Four times higher incidence of ESRD in African Americans compared to European Americans.

18- to 50-fold increased risk for HIV-1–associated focal segmental glomerulosclerosis (FSGS).

Hypothesis - susceptibility alleles for ESRD have a higher frequency in the West African than the European gene pool.

Design – A genome-wide admixture scan in cases and controls

# Genetics of End-Stage Renal Disease

Large freq difference for haplotype E-1  
(60% in AA vs 4% in EA)

For none carriers of haplotype E-1, the population frequency of sporadic FSGS is very similar between AA (0.06%) and EA (0.05%) suggesting that the two populations have comparable background levels of susceptibility to FSGS in the absence of MYH9 genetic susceptibility.

MYH9 may account for 66–100% of the disparity in susceptibility to focal segmental glomerulosclerosis (FSGS).

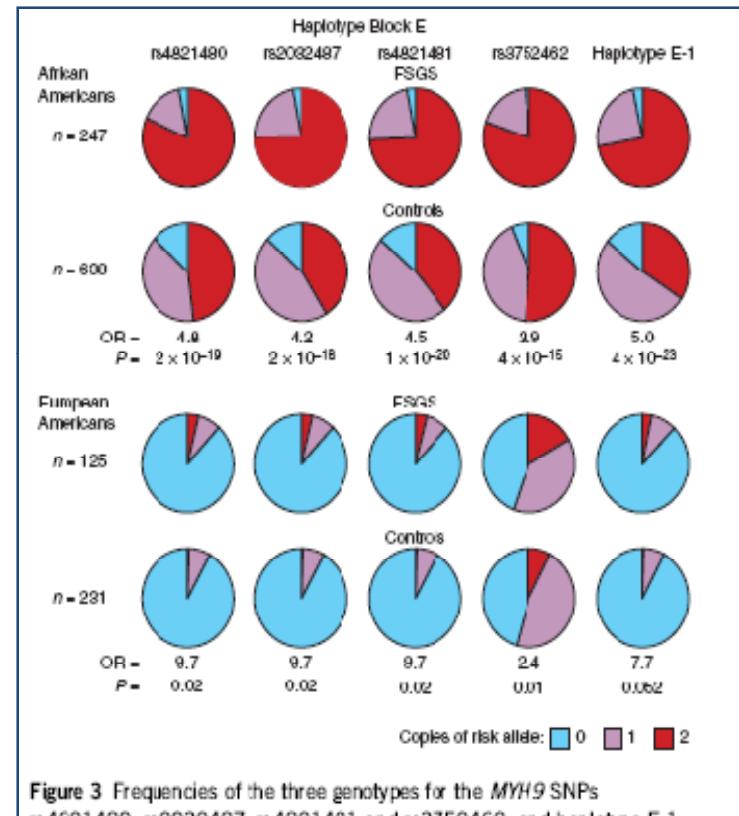


Figure 3 Frequencies of the three genotypes for the MYH9 SNPs rs4821480, rs2032487, rs4821481 and rs3752462, and haplotype E-1, the most frequent haplotype containing the four SNPs, in African American and European American FSGS cases and controls. Odds ratios and P values for the recessive model comparing FSGS cases and controls are shown.

### Association of Trypanolytic ApoL1 Variants with Kidney Disease in African-Americans

Giulio Genovese,<sup>1,2\*</sup> David J. Friedman,<sup>1,3\*</sup> Michael D. Ross,<sup>4</sup> Laurence Lecordier,<sup>5</sup> Pierrick Uzureau,<sup>5</sup> Barry I. Freedman,<sup>6</sup>

Showed that in African-Americans, focal segmental glomerulosclerosis (FSGS) and hypertension-attributed end-stage kidney disease (HESKD) are associated with two independent sequence variants (*G1* and *G2*) in the apolipoprotein L-1 (*APOL1*) gene on chromosome 22

FSGS odds ratio = 10.5 (95% CI: 6.0-18.4);

H-ESKD odds ratio = 7.3 (95% CI 5.6-9.5).

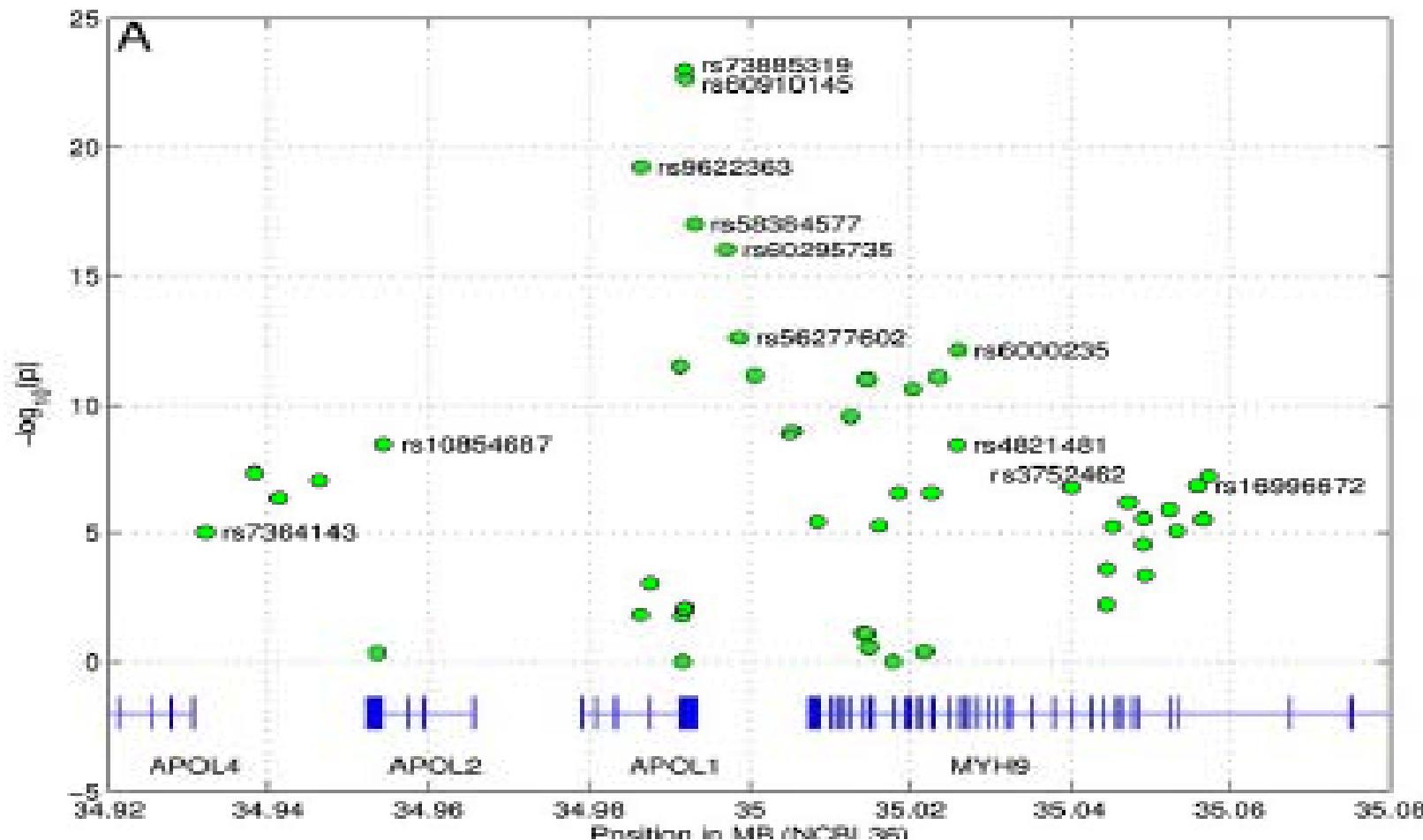
The two *APOL1* variants are common in African chromosomes but absent from European chromosomes. The variants reside within haplotypes that harbor signatures of positive selection.

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

Speculated that evolution of a critical survival factor in Africa may have contributed to the high rates of renal disease in African-Americans.

### Association of Trypanolytic ApoL1 Variants with Kidney Disease in African-Americans

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Controlling for multiple sets of variants in *MYH9* failed to eliminate the *APOL1* signal.

The LD patterns in this region show that G1 (a two-allele haplotype) and G2 (6 base pair deletion) are in strong LD with variants in *MYH9*.

The *MYH9 E-1* haplotype, the best predictor of renal disease in previous studies, is present in most haplotypes containing the G1 or G2 allele.

E-1 is present in 89% of haplotypes carrying G1 and in 76% of haplotypes carrying G2, explaining the association of *MYH9 E-1* with renal disease.

## Allele frequencies for GWAS signals of selected diseases in four HapMap populations of African ancestry

Disease	Number of loci	Median of MAF	Range of MAF
Type 2 Diabetes	38	0.261	0.026 - 0.641
Crohn's Disease	47	0.261	0.018 - 0.792
SLE	20	0.206	0.031 - 0.673
Psoriasis	14	0.191	0.043 - 0.647
Breast Cancer	16	0.259	0.055 - 0.634
Prostate Cancer	23	0.279	0.039 - 0.795

Adapted from Adeyemo & Rotimi, *Public Health Genomics*, 2010  
Charles Rotimi - crggh.nih.gov

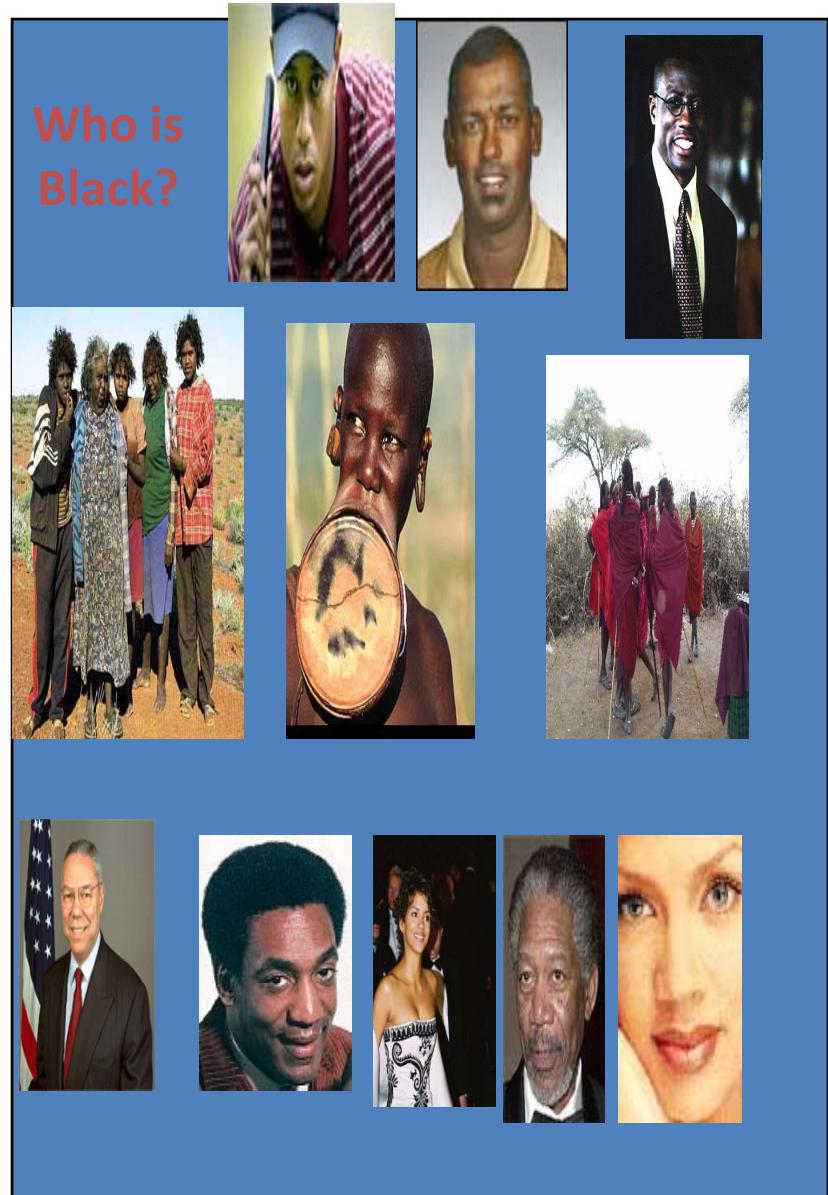
# Pharmacogenomics

**The danger of group labeling of  
genetic variation**

# Variable Drug Response

- How do we interpret differential drug response by “groups” when “group” definition is imprecise, fluid and time dependent?
- Can we tell how an individual will respond based on group data?

**Confusion:** Group identity is confused with group ancestry. For example, the group identity “African Americans” does not reflect a single path of ancestry.



# 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

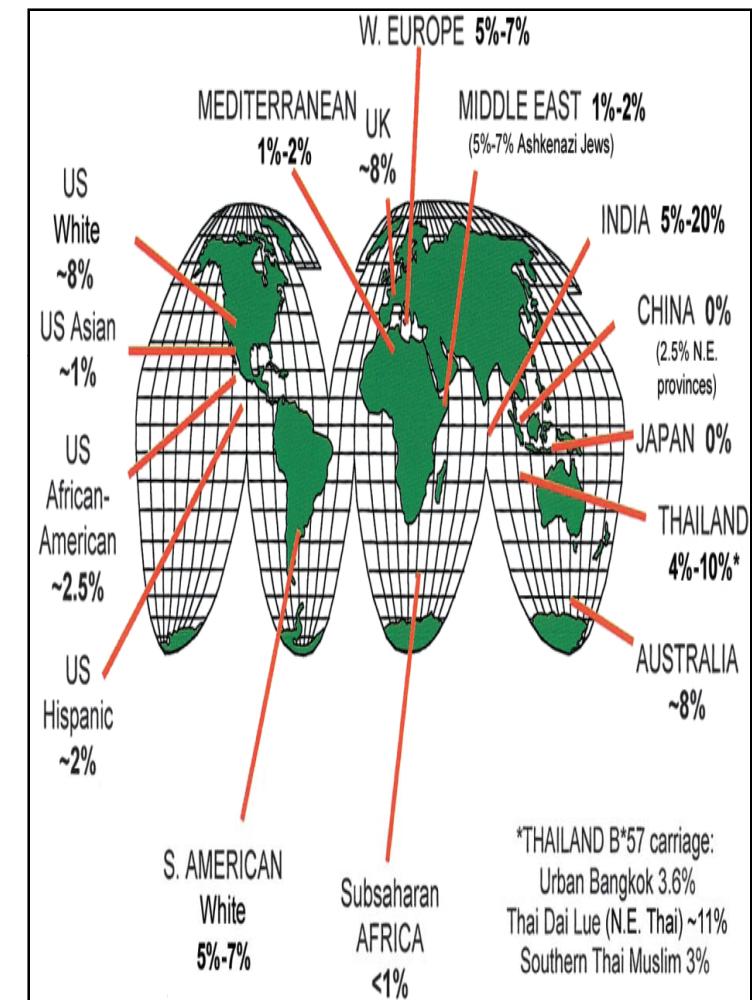
Indians - highest freq of 17.6% - 20%.

Africa - 13.6% (Maasai), 0% (Yoruba).

Europe – 3.4% (Tuscans), 5.8% (Utah).

**The label “Africans” or “Blacks” renders radically different allele frequencies invisible.**

Consequence - Wrong public health decision about who to screen.

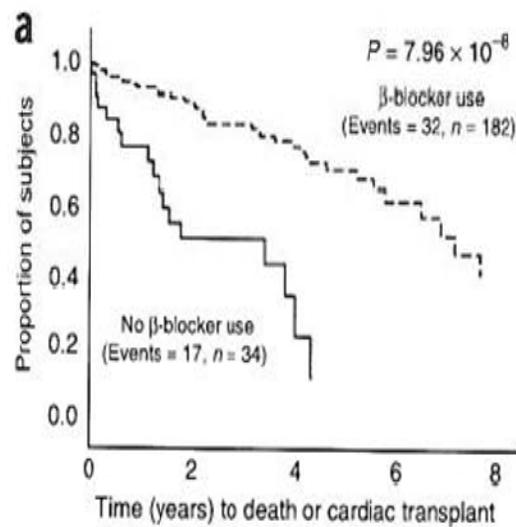


CID 2006:43 (1 July) • HIV/AIDS

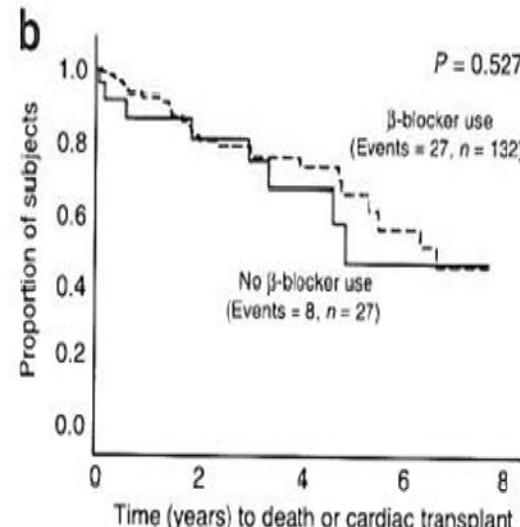
# A GRK5 polymorphism that inhibits $\beta$ -adrenergic receptor signaling is protective in heart failure

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.**

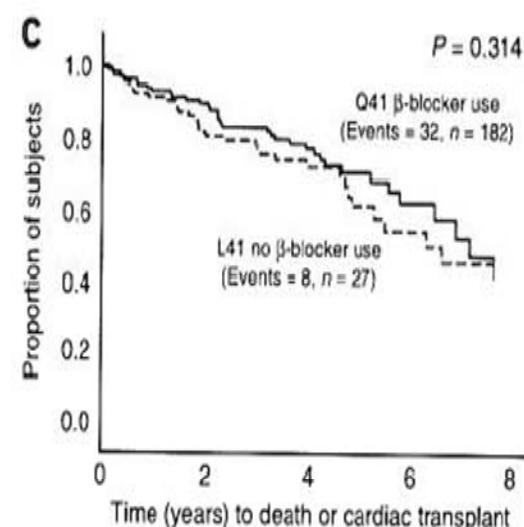
GRK5-Q41 only - with and without  $\beta$ -blocker use



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



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



# Genome-wide patterns of population structure and admixture in West Africans and African Americans

Katarzyna Bryc<sup>a</sup>, Adam Auton<sup>a</sup>, Matthew R. Nelson<sup>b</sup>, Jorge R. Oksenberg<sup>c</sup>, Stephen L. Hauser<sup>c</sup>, Scott Williams<sup>d</sup>, Alain Froment<sup>e</sup>, Jean-Marie Bodo<sup>f</sup>, Charles Wambebe<sup>g</sup>, Sarah A. Tishkoff<sup>h,1,2</sup>, and Carlos D. Bustamante<sup>a,1,3</sup>

That some individuals who self-identify as African American show almost no West African ancestry and others show almost complete West African ancestry has implications for pharmacogenomics studies and assessment of disease risk. Although individuals with very low West African or very low European ancestry may be expected by chance after several generations of admixture, these individuals are most likely descendants of individuals of European ancestry or recent African immigrants, respectively. Assuming these individuals are not simply mislabeled, it appears that the range of genetic ancestry captured under the term *African American* is extremely diverse, which suggests caution should be used in prescribing treatment based on differential guidelines for African Americans (45).

# Take Home Message

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

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**RACE**  
Are We So Different?™



A Project of the American Anthropological Association

**“Race, in countries like the US at least, is a fuzzy social construct by which people with one or two superficial similarities are often clumped together. It reflects simplistic cultural habits reinforced by the questionable practices of government statisticians and medical researchers, among others. Ethnic binning may simplify thought processes and, in some cases, negate them altogether. But using genetics to define race is like slicing soup. You can cut wherever you want, but the soup stays mixed.”**

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## Press Briefing on Human Heredity and Health in Africa

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## Press Briefing on Human Heredity and Health in Africa

Announcement of partnership between NIH and Wellcome Trust to fund population-based genomic studies in Africa.

June 22, 2010

6 a.m. Eastern Daylight Savings Time (11 a.m., British Summer Time)

[watch in HD](#)

Charles Rotimi - crggh.nih.gov

# Human Heredity and Health in Africa - H3Africa

## June 22, 2010 – London, England



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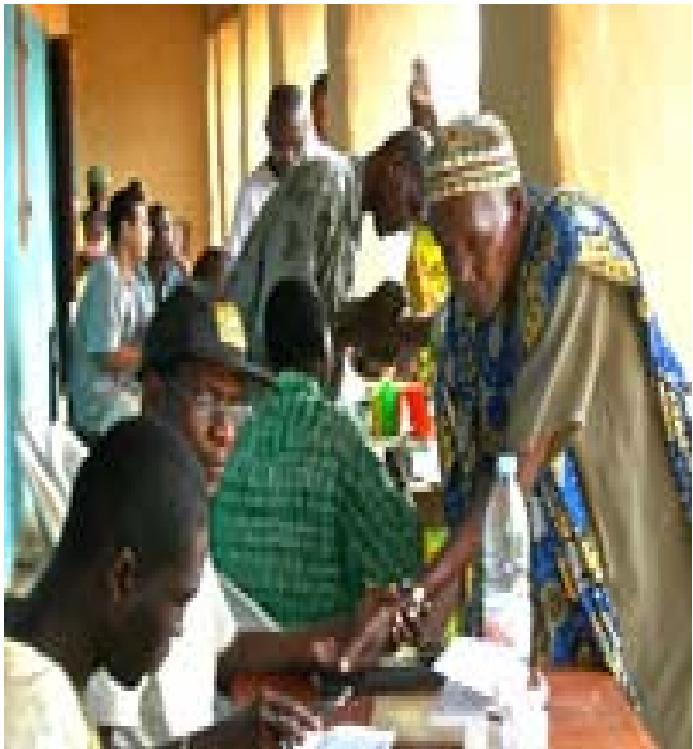


gentlemen, welcome to the Wellcome Trust H3  
Africa H3 Africa media briefing conference

<http://www.youtube.com/watch?v=G0H8KwmWaAY>

Charles Rotimi - crggh.nih.gov

# Human Heredity and Health in Africa - H3Africa



**The National Institutes of Health and the Wellcome Trust, a British charity in London, has announced a partnership to launch a project called H3Africa.**

H3Africa will conduct a number of population-based studies, using genomic and clinical tools, to identify the genetic and environmental contributions to communicable and non-communicable diseases.

NIH has pledged \$25 million over five years; the Wellcome Trust has pledged an additional \$12 million. The partnership includes the African Society of Human Genetics. <http://www.genome.gov/>

# SURVIVAL INSTINCT AND THE FLUIDITY OF SELF AND GROUP IDENTITY

## THE AIRPLANE JOKE: AN AEROPLANE IS FLYING OVER THE USA.

- THE PILOT SAYS: "THE PLANE IS LOSING HEIGHT AND ALL THE BAGGAGE MUST BE THROWN OUT."
- WE'RE STILL LOSING HEIGHT, WE MUST THROW THINGS OUT FROM THE CABIN
- DESPITE THINGS BEING THROWN OUT, THE PLANE CONTINUES ITS DESCENT.
- PILOT: "STILL GOING DOWN, WE MUST THROW OUT SOME PEOPLE."
- THERE'S A BIG GASP FROM THE PASSENGER'S.
- PILOT: "BUT TO MAKE THIS FAIR, PASSENGERS WILL BE THROWN OUT IN ALPHABETICAL ORDER:
  - A. ANY AFRICANS ON BOARD? NO-ONE MOVES.
  - B. ANY BLACKS ON BOARD?" NO-ONE MOVE'S
  - C. ANY CARIBBEANS ON BOARD?" STILL NO-ONE MOVES.
- A LITTLE BLACK BOY ASKS HIS DAD: "DAD. WHAT ARE WE?" DAD: "SON, TONIGHT WE ARE ZULUS"