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
The central mission of the CRGGH, 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.

Charles Rotimi - crggh.nih.gov
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

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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

Grundy SM Nature Review 2006

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Genomics and Population Differences in Disease Distribution (Health Disparities)

Genomics (genes) - one piece of the puzzle.

- **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

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.
Impact of Social Policy on Health Disparities

Incarceration rates comparing Blacks & Whites

<table>
<thead>
<tr>
<th>Year</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1933</td>
<td>2.5:1</td>
</tr>
<tr>
<td>1950</td>
<td>4.0:1</td>
</tr>
<tr>
<td>1960</td>
<td>5.0:1</td>
</tr>
<tr>
<td>1970</td>
<td>6.0:1</td>
</tr>
<tr>
<td>1989</td>
<td>7.0:1</td>
</tr>
<tr>
<td>1995</td>
<td>8.0:1</td>
</tr>
</tbody>
</table>

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.”

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

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Genomic Science

Enabling Fundamental Insight into biology and Human History

Medical and Public Health Applications are in their infancy but growing
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 titling arrays, which measure transcription without regard to existing annotation, indicates that much of intergenic DNA (“JUNK DNA”) is also transcribed.


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 and may be revised substantially in the future.
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?
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.

McClellan J and King MC: Cell 2010
The Genetic Structure and History of Africans and African Americans

Sarah A. Tishkoff,† Floyd A. Reed,†† Françoise R. Friedlaender,‡ Christopher Ehret

• 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”).

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

SCIENCE VOL 324 22 MAY 2009
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\(^1\)*, Patrick Varilly\(^1\)*, Ben Fry\(^1\), Jason Lohmueller\(^1\), Elizabeth Hostetter\(^1\), Chris Cotsapas\(^1,2\), Xiaohui Xie\(^1\), Elizabeth H. Byrne\(^1\), Steven A. McCarroll\(^1,2\), Rachelle Gaudet\(^3\), Stephen F. Schaffner\(^1\), Eric S. Lander\(^1,4,5,6\) & The International HapMap Consortium\(^\dagger\)

<table>
<thead>
<tr>
<th>Population</th>
<th>Gene</th>
<th>Selection Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibadan, Nigeria</td>
<td>LARGE, DMD</td>
<td>Infection – Lassa virus</td>
</tr>
<tr>
<td>Utah, USA</td>
<td>SCL24A5, SLC45A2</td>
<td>Skin Pigmentation in Europe</td>
</tr>
<tr>
<td>China/Japan</td>
<td>EDAR &amp; EDA2R (Ectodysplasin pathway)</td>
<td>Development of hair follicles in Asia</td>
</tr>
</tbody>
</table>

*Charles Rotimi - crg3@mit.edu*

Diet and the evolution of human amylase gene copy number variation

George H Perry¹,², Nathaniel J Dominy³, Katrina G Claw¹,⁴, Arthur S Lee³, Heike Fiegler⁵, Richard Redon⁵,

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.\(^1\)

The bar chart depicts the mean copy number per sample, with an interval of two standard errors about 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).
Complete Khoisan and Bantu genomes from southern Africa

Stephan C. Schuster1*, Webb Miller1*, Aakrosh Ratan1, Lynn P. Tomsho1, Belinda Giardine1, Lindsay R. Kasson1,

"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.

Charles Rotimi - crggh.nih.gov
Using Genomic Tools to Understand Disease etiology and disparities
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

Genomewide Association Studies and Assessment of the Risk of Disease

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

Figure 1. The Genomewide Association Study.
Genomewide Association Studies and Assessment of the Risk of Disease

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

800 SNPs in 545 studies as of March, 2010
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.  

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gene</th>
<th>Function or Pathway</th>
<th>Source of Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-related macular degeneration</td>
<td>CFH</td>
<td>Complement-mediated inflammation</td>
<td>Klein et al.²⁵</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>CDKN2A, CDKN2B</td>
<td>Cell-cycle regulator</td>
<td>Helgadottir et al.³⁶</td>
</tr>
<tr>
<td>Childhood asthma</td>
<td>ORMDL3</td>
<td>Unknown</td>
<td>Moffatt et al.³⁷</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>CDKAL1</td>
<td>Cell-cycle regulator</td>
<td>Scott et al.³</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>ATG16L1</td>
<td>Autophagy</td>
<td>Rioux et al.³⁸</td>
</tr>
</tbody>
</table>
Overlap of genetic risk factor loci for common diseases.

Metabolic diseases and cancer
- Type 2 diabetes
- Triglyceride levels
- Prostate cancer
- Colon cancer

Genes
- IL23R
- CDKAL1
- PTPN22
- STAT4
- GCKR
- JAZF1
- HNF1B
- TCF7L2

Autoimmune diseases
- Crohn’s disease
- Psoriasis
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Type 1 diabetes
- Graves’ disease

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

The International HapMap Consortium*

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## Table 3 | Number of tag SNPs required to capture common (MAF ≥ 0.05)

### Phase II SNPs

<table>
<thead>
<tr>
<th>Threshold</th>
<th>YRI</th>
<th>CEU</th>
<th>CHB+JPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r^2 ≥ 0.5$</td>
<td>627,458</td>
<td>290,969</td>
<td>277,831</td>
</tr>
<tr>
<td>$r^2 ≥ 0.8$</td>
<td>1,099,422</td>
<td>552,853</td>
<td>520,111</td>
</tr>
<tr>
<td>$r^2 = 1$</td>
<td>1,616,739</td>
<td>1,024,665</td>
<td>1,078,959</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Platform</th>
<th>Yoruba (YRI)</th>
<th>CEU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affymetrix 500K</td>
<td>$r \geq 0.8$ (%)</td>
<td>46</td>
</tr>
<tr>
<td>Affy Array 6.0</td>
<td>$r \geq 0.8$ (%)</td>
<td>66</td>
</tr>
<tr>
<td>Illumina HumanHap550</td>
<td>$r \geq 0.8$ (%)</td>
<td>55</td>
</tr>
<tr>
<td>Illumina HumanHap650Y</td>
<td>$r \geq 0.8$ (%)</td>
<td>66</td>
</tr>
</tbody>
</table>

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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

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

\(^a\) Total participants include participants in studies that include data from multiple ethnic groups.

\(^b\) European includes participants of European ancestry.

\(^c\) Mixed includes participants of mixed ancestry.

\(^d\) Total participants include participants in studies that include data from multiple ethnic groups.

\(^e\) European includes participants of European ancestry.

\(^f\) Other includes participants of other ancestry.

\(^g\) Papua-New Guinean includes participants of Papua-New Guinean ancestry.
A Genome-Wide Association Study of Hypertension and Blood Pressure in African Americans

Adebowale Adeyemo, Norman Gerry, Guanjie Chen, Alan Herbert, Ayo Doumatey, Hanxia Huang, Jie Zhou, Kerrie Lashley, Yuanxiu Chen, Michael Christian, Charles Rotimi

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 Wistar 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 1,071 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 CACAN1AH. Two of these genes, SLC24A4 (a sodium/potassium/calcium exchanger) and CACAN1AH (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 rs1967226, p = 5.8 x 10^-7) or with hypertension as a binary trait (top scoring SNP rs9791170, p = 1.4 x 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 suggest 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.

<table>
<thead>
<tr>
<th>Rank</th>
<th>SNP</th>
<th>Chr</th>
<th>Position</th>
<th>Type</th>
<th>Closest gene</th>
<th>Distance to gene (kb)</th>
<th>Allele</th>
<th>MAF</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rs5743185</td>
<td>2</td>
<td>190446083</td>
<td>INTRONIC</td>
<td>PMS1</td>
<td>0</td>
<td>T</td>
<td>0.1418</td>
<td>2.09E-11</td>
</tr>
<tr>
<td>2</td>
<td>rs16877320</td>
<td>6</td>
<td>16931005</td>
<td>INTERGENIC</td>
<td>AL365265.23</td>
<td>12</td>
<td>G</td>
<td>0.1316</td>
<td>3.42E-09</td>
</tr>
<tr>
<td>3</td>
<td>rs11160059</td>
<td>14</td>
<td>91877083</td>
<td>INTRONIC</td>
<td>SLC24A4</td>
<td>0</td>
<td>A</td>
<td>0.1785</td>
<td>1.54E-08</td>
</tr>
<tr>
<td>4</td>
<td>rs17365948</td>
<td>8</td>
<td>102026053</td>
<td>INTRONIC</td>
<td>YWHA2</td>
<td>0</td>
<td>A</td>
<td>0.1125</td>
<td>1.59E-08</td>
</tr>
<tr>
<td>5</td>
<td>rs12242022</td>
<td>11</td>
<td>95868689</td>
<td>INTRONIC</td>
<td>IPO4</td>
<td>0</td>
<td>A</td>
<td>0.1251</td>
<td>4.80E-08</td>
</tr>
<tr>
<td>6</td>
<td>rs3751664</td>
<td>16</td>
<td>1194370</td>
<td>NON_SYNONYMOUS_CODING</td>
<td>CACAN1H</td>
<td>0</td>
<td>T</td>
<td>0.1093</td>
<td>6.71E-08</td>
</tr>
<tr>
<td>7</td>
<td>rs1165639</td>
<td>18</td>
<td>55318592</td>
<td>INTERGENIC</td>
<td>MC4R</td>
<td>127</td>
<td>C</td>
<td>0.0977</td>
<td>2.12E-07</td>
</tr>
<tr>
<td>8</td>
<td>rs4613079</td>
<td>16</td>
<td>79201458</td>
<td>INTRONIC</td>
<td>CDGYL2</td>
<td>0</td>
<td>T</td>
<td>0.1766</td>
<td>5.06E-07</td>
</tr>
<tr>
<td>9</td>
<td>rs18201744</td>
<td>6</td>
<td>60718174</td>
<td>INTERGENIC</td>
<td>PTEN</td>
<td>17</td>
<td>A</td>
<td>0.16</td>
<td>1.12E-06</td>
</tr>
<tr>
<td>10</td>
<td>rs2107272</td>
<td>7</td>
<td>70401493</td>
<td>INTERGENIC</td>
<td>PMI</td>
<td>15</td>
<td>T</td>
<td>0.4292</td>
<td>1.21E-06</td>
</tr>
</tbody>
</table>
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.
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 (FEV₁) 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 FEV₁) in 4 to 5% of participants.
Genetic Ancestry in Lung-Function Predictions

**Figure 1.** Ancestry, Forced Expiratory Volume in 1 Second (FEV₁), and Differences in Predicted FEV₁ 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.)
Importance of Ancestry in Genomic Studies

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.
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 \textit{IL28B} and spontaneous clearance of hepatitis C virus

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

Nature – Oct 8, 2009

\textbf{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


<table>
<thead>
<tr>
<th>Population Groups</th>
<th># of individuals (# of populations)</th>
<th>Mean Frequency</th>
<th>Frequency Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>428 (10)</td>
<td>36.2</td>
<td>23.1 – 54.8</td>
</tr>
<tr>
<td>Europe</td>
<td>761 (13)</td>
<td>68.35</td>
<td>52.8 – 85.7</td>
</tr>
<tr>
<td>East Asia</td>
<td>380 (8)</td>
<td>94.93</td>
<td>90.0 – 100.0</td>
</tr>
</tbody>
</table>

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 – Oct 8, 2009

Charles Rotimi - crggh.nih.gov
Prostate Cancer

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 Kopp¹,¹⁷, Michael W Smith²,¹⁶,¹⁷, George W Nelson²,¹⁷, Randall C Johnson², Barry I Freedman³,

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

W H Linda Kao¹−³,²⁵, Michael J Klag¹−³,²⁵, Lucy A Meoni²−⁴, David Reich⁵,⁶, Yvette Berthier-Schaad¹,

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 A A (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).
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

Giulio Genovese,¹,²,³ David J. Friedman,¹,³,⁴ Michael D. Ross,⁴ Laurence Lecordier,⁵ Pierrick Uzureau,⁵ Barry I. Freedman,⁶
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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of loci</th>
<th>Median of MAF</th>
<th>Range of MAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 Diabetes</td>
<td>38</td>
<td>0.261</td>
<td>0.026 - 0.641</td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td>47</td>
<td>0.261</td>
<td>0.018 - 0.792</td>
</tr>
<tr>
<td>SLE</td>
<td>20</td>
<td>0.206</td>
<td>0.031 - 0.673</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>14</td>
<td>0.191</td>
<td>0.043 - 0.647</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>16</td>
<td>0.259</td>
<td>0.055 - 0.634</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>23</td>
<td>0.279</td>
<td>0.039 - 0.795</td>
</tr>
</tbody>
</table>

Adapted from Adeyemo & Rotimi, Public Health Genomics, 2010
Pharmacogenomics

The danger of group labeling of genetic variation

Charles Rotimi - crggh.nih.gov
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

Charles Rotimi - crggh.nih.gov
A GRK5 polymorphism that inhibits β-adrenergic receptor signaling is protective in heart failure

1. G protein-coupled receptor kinases (GRKs) desensitize β-adrenergic receptors (βARs).
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 β-blocker. **β-blockers are absolutely effective in AA without the variant.**

Liggett SB et al. Nat. Medicine April 2008
Genome-wide patterns of population structure and admixture in West Africans and African Americans

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

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).

www.pnas.org/cgi/doi/10.1073/pnas.0909559107
Take Home Message

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

Nature Biotechnology

Charles Rotimi - crggh.nih.gov
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)
Human Heredity and Health in Africa - H3Africa

Press Briefing on Human Heredity and Health in Africa

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/

Charles Rotimi - crggh.nih.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"