Precision Medicine and Health Disparities: The Promise and Perils of Emerging Technologies

Charles N. Rotimi, PhD

Director: Center for Research on Genomics and Global Health
Chief and Senior Investigator: Metabolic, Cardiovascular and Inflammatory Disease Genomics Branch
Many forms of Health Disparities

1. Ethnicity/Ancestry

African Americans make up 13 percent of the U.S. population ...

... but represent almost half of all new HIV cases.


2. Age, gender & ancestry

Prevalence of Hypertension – Aged 18 and over, US 2011-2012

https://www.cdc.gov/nchs/data/databriefs/db133.pdf
3. Geography & ancestry

Prevalence of hypertension – Seven populations of West African origin

![Bar chart showing prevalence of hypertension among different populations.]

Prevalence of hypertension among urban and rural Yoruba individuals in Nigeria

![Graph showing prevalence of hypertension over age.]

4. Socioeconomic (poor vs rich)

Production of aflatoxin by Aspergillus flavus in some Nigerian indigenous beverages and foodstuffs. *Mycopathologia* 1980

Rotimi C et al., 1980

[Chemical structure of aflatoxin]
The Death Gap – David A Ansell, MD

He reveals the profound inequalities, particularly racial inequalities, that generate tremendous differences in lifespan and well-being across neighborhoods, and he provides powerful patient anecdotes that provide a human face to otherwise abstract challenges.” Harold Pollack, University of Chicago

Location, Location, Location – real estate
These are also the three most important words in understanding health and wealth inequality in America

Life Expectancy varies greatly by neighborhoods in Chicago

<table>
<thead>
<tr>
<th>Neighborhoods</th>
<th>Income</th>
<th>Life expectancy</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Loop</td>
<td>$80,000</td>
<td>85yrs</td>
<td>Affluent downtown</td>
</tr>
<tr>
<td>North Lawndale</td>
<td>$25,000</td>
<td>72yrs</td>
<td>91% AA (5 miles from the Loop)</td>
</tr>
<tr>
<td>Hyde Park</td>
<td>$40,000</td>
<td>83yrs</td>
<td>Racially diverse</td>
</tr>
<tr>
<td>Washington Park</td>
<td>$22,000</td>
<td>69yrs</td>
<td>Almost entirely AA</td>
</tr>
</tbody>
</table>

AA – African Americans

The major drivers of health disparities (inequalities) at the national and global levels are not genetic.

The wages and benefits we're paid, the neighborhoods we live in, the schools we attend and our tax policies are health issues every bit as critical as diet, smoking and exercise.

The unequal distribution of social factors that drive health disparities are not natural or inevitable. They are the result of choices that we as a community, as states, and as a nation have made, and can make differently. 

Larry Adelman, Unnatural Causes March 27, 2008

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

- Charles Darwin

Why study genetics/genomics in the context of health disparities?

Our Genomes – A history book that has unbiasedly capture human experiences over thousands of years.

What is this book teaching us about human history & Health?
Reducing the Global Genomic Inequity Gap: Development of an African Genome Project

Melanie J. Newport, Charles N. Rotimi


Concern that the equity gap that already exists between developed and developing countries will be widened if developing country populations, their scientists and health practitioners are not fully engaged in the application of genomic tools to address global problems including health and food production.

Tomorrow’s Medicine and Technology may not work for all human populations
Human Migrational History

1. Studied ancestry of 5,966 humans from 30 language families
2. Identified 21 ancestries; Majority (97.3%) have mixed ancestry
3. Ubiquity of mixed ancestry emphasizes the importance of accounting for ancestry in history, forensics, and health.

Using genetics to define racial group is like slicing soup. You can cut wherever you want, but the soup stays mixed.  
*Nature Biotechnology 2001*

Although “race” and thus racial groups may be difficult to define genetically, the impact of racism is real

**Racism is a fundamental driver of inequalities in societies where it exists.**
Mutations common in African Americans (2%); Rare in European Americans (<0.1%) Associated with 40% reduction in LDL-C level

The label “Africans” or “Blacks” renders radically different HLA-B*5701 allele frequencies invisible.

Fine-Mapping: showing how smaller haplotype blocks in African ancestry populations helped refine genome-wide significant loci

Graft survival shorter in donor kidneys with 2 APOL1 risk variants (HR 3.8, p=0.008)
No difference by overall African ancestry

“Anytime different outcomes exist for kidney disease in African-Americans and European-Americans, an APOL1 influence needs to be investigated,” says Barry Freedman.

Health disparities in the genomic era: the case for diversifying ethnic representation

Charles N Rotimi

Genome Medicine 2012, 4:65


Rotimi C et al.

Human Molecular Genetics, 2017
The Africa Society of Human Genetics (AfSHG) was formed to ensure that Africa is not left out of the genomic revolution.

Annual meeting of the African Society of Human Genetics - Nov 2007, Cairo, Egypt

Human Heredity and Health in Africa (H3Africa)
London, England; June 22, 2010

Vision for H3Africa

To enhance capacity for using contemporary research approaches, in Africa by African scientists, to understand the genetic and environmental factors that determine disease susceptibility and drug responses in Africans.

A key aspect of H3Africa - Awards are made directly to African Institutes & PIs
Before H3Africa: Minimum Collaboration Between African Scientists

Enabling the genomic revolution in Africa

H3Africa is developing capacity for health-related genomics research in Africa

By The H3Africa Consortium†

Our understanding of genome biology, genomics, and disease, and even human history, has advanced tremendously with the completion of the Human Genome Project. Technological advances coupled with significant cost reductions in genomic research have yielded novel insights into disease etiology, diagnosis, and therapy for some of the world’s most intractable and devastating diseases—including malaria, HIV/AIDS, tuberculosis, cancer, and diabetes. Yet, despite the burden of infectious diseases and

>$76 million of funding  27 African countries
>$75,000 research participants  >500 investigators  25 research projects

African Center of Excellence for Infectious diseases Genomics
Redeemer’s University, Nigeria

Establishing research programs for African scientists to pursue high-impact projects
Funded by H3Africa & World Bank

Genomic surveillance elucidates Ebola virus origin and transmission during the 2014 outbreak

“Because we have sophisticated genomics research laboratories at the African Centre of Excellence for Genomics of Infectious Diseases, in Redeemer’s University, we were able to quickly diagnose the virus within hours of receiving the sample of the first Ebola index case in Nigeria”

H3Africa Pan-African 2.5M Consortium Array
1. Extensive African-enriched reference panel
2. Based on sequencing of thousands of diverse individuals across Africa
3. 8 populations that have not been previously sequenced
4. Substantial improvement in sensitivity for African GWAS
5. H3Africa & Illumina collaboration
Sickle Cell Disease

- The first “molecular” disease
  - Caused by point mutation in the β-globin chain of hemoglobin
  - {VM Ingram 1956 Nature 178:792}

**NORMAL β-GLOBIN**

<table>
<thead>
<tr>
<th>DNA</th>
<th>TGA</th>
<th>GGA</th>
<th>CTC</th>
<th>CTC</th>
<th>..........</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRNA</td>
<td>ACU</td>
<td>CCU</td>
<td>GAG</td>
<td>GAG</td>
<td>..........</td>
</tr>
<tr>
<td>Amino acid</td>
<td>thr</td>
<td>pro</td>
<td>glu</td>
<td>glu</td>
<td>..........</td>
</tr>
</tbody>
</table>

**MUTANT β-GLOBIN**

<table>
<thead>
<tr>
<th>DNA</th>
<th>TGA</th>
<th>GGA</th>
<th>CAC</th>
<th>CTC</th>
<th>..........</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRNA</td>
<td>ACU</td>
<td>CCU</td>
<td>GUG</td>
<td>CTC</td>
<td>..........</td>
</tr>
<tr>
<td>Amino acid</td>
<td>thr</td>
<td>pro</td>
<td>val</td>
<td>glu</td>
<td>..........</td>
</tr>
</tbody>
</table>

“the point mutation in the β-globin chain of hemoglobin, causes the hydrophilic amino acid glutamic acid to be replaced with the hydrophobic amino acid valine at the sixth position

**Epidemiology**

- 1 in 5000 Americans, 1 in 500 African Americans
- 1 in 36,000 Hispanic Americans
- Disparity solely due to genetics

**Treatment**

- 1970s: opioids for pain management
- 1990s: hydroxyurea (increases HbF levels)
- 2017: L-glutamine second FDA-approved drug (“to reduce severe complications”)
- Blood transfusions
- Inactivation of BCL11A reactivates HbF (no therapeutic way to achieve this) {J Xu et al. Science 2011 case-gene 1st therapy trial 2017 No crises or adverse events after 15 months
Whole genome sequence-based haplotypes reveal single origin of the sickle allele during the Holocene Wet Phase

Daniel Shriner, Charles N. Rotimi

1. Five classical designations of sickle haplotypes are based on the presence/absence of restriction sites; named after ethnic groups or geographic origin of patients

2. Two models of the origin of the sickle allele
   a. **Multicentric** - five independent occurrences of the same mutation
   b. **Unicentric** - single older occurrence

3. Analyzed Whole Genome Sequence data from 1000 Genomes Project, African Genome Variation Project, and Qatar Genome project
4. Infer a single origin of the sickle allele ~ 7,300 years ago during Holocene Wet Phase or Green Sahara
5. We established a new haplotypic classification based on three clusters
   a. Central African Republic/Bantu + Cameroon
   b. Senegal
   c. Benin + Senegal
6. Senegal designation is substructured into two clusters, one shared with the Benin designation
7. Substructuring of haplotypes potentially confounded previous assessments of clinical phenotype or disease severity

[https://www.biorxiv.org/content/early/2017/09/12/187419](https://www.biorxiv.org/content/early/2017/09/12/187419)
Serious negative consequences of a physician’s assumptions about a patient’s race

8-year-old boy, phenotypically European, presented with acute abdominal pain and anemia (hematocrit, 0.21).

Although his body temperature was only 37.9 °C, surgery was considered. A technician found red corpuscles with hemolytic characteristics on a smear.

Surgery was canceled after the results of a subsequent sickle preparation were found to be positive, and the child was treated for previously undiagnosed sickle cell anemia.

His parents were from Grenada and were of Indian, northern European, and Mediterranean ancestry.

We must all go to the tailor so that our genomic clothing (precision medicine) will fit properly as we use genetics/genomics to understand disease etiology and develop new treatment strategies.

The Era of Precision Medicine

Who is Black?

Naomi Osaka – Haitian father and Japanese mother

Vijay Singh – Nationality: Fijian

African Diaspora Populations
Range of individual African admixture proportion- 0% to 97.8%
Range of Native American ancestry - 0% to 100%

How do we interpret differential drug response by “groups” when “group” definition is imprecise, fluid and time dependent?
Gene-Based Sequencing Identifies Lipid-Influencing Variants with Ethnicity-Specific Effects in African Americans

Amy R. Bentley, Guanjie Chen, Daniel Shriner, Ayo P. Doumateau, Jie Zhou, Hanxia Huang, James C. Mullikin, Robert W. Blakesley, Nancy F. Hansen, Gerard G. Bouffard, Praveen F. Cherukuri, Baishali Maskeri, Alice C. Young, Adebowale Adeyemo, Charles N. Rotimi

Sequenced 5 genes (ABCA1, LCAT, LPL, PON1, and SERPINE1) for variant discovery in African Americans with extreme lipids.

Follow-up in population-based sample of African Americans (n=1694)

Association of LPL variants (rs328) depended on ancestry at that locus.
Pharmacogenomics, ancestry and clinical decision making for global populations

E Ramos, A Doumatej, AG Elkahloun, D Shrinker, H Huang, G Chen, J Zhou, H McLeod, A Adeyemo and CN Rotimi

The DMET™ Plus Solution

Markers indicate location of sample collection.

Warfarin Dosing

<table>
<thead>
<tr>
<th>Mean dose</th>
<th>Haplotype</th>
<th>Non-African Ancestry</th>
<th>African Ancestry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CEU</td>
<td>CHB</td>
</tr>
<tr>
<td>40.15</td>
<td>TTGGC</td>
<td>0.36</td>
<td>0.05</td>
</tr>
<tr>
<td>35.24</td>
<td>TCGGC</td>
<td>0.24</td>
<td>--</td>
</tr>
<tr>
<td>26.41</td>
<td>TCAAT</td>
<td>0.37</td>
<td>0.11</td>
</tr>
<tr>
<td>23.86</td>
<td>CCAAT</td>
<td>0.03</td>
<td>0.83</td>
</tr>
<tr>
<td>??</td>
<td>TCAGC</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

The Pharmacogenomics Journal (2014) 14, 217–222
1. Hepatitis C virus infection affects 170 million people worldwide; leading cause of cirrhosis.

2. Treatment - 48-week course of peginterferon-alpha-2b or -alpha-2a combined with ribavirin

3. Patients of European ancestry have higher probability of being cured compared to 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.

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.
Precision Medicine

More Precise Accounting for Individual Variability

Most guide against over promise especially in the context of health disparities

Our Diversity is not an illusion.

We need to study how our genetic backgrounds increase our susceptibility/resistance to disease

This may shed novel insight into Health Disparities
Many persons contributed to this presentation

Special thanks to Daniel Shriner for the sickle cell slides

Thanks
Glad to take questions