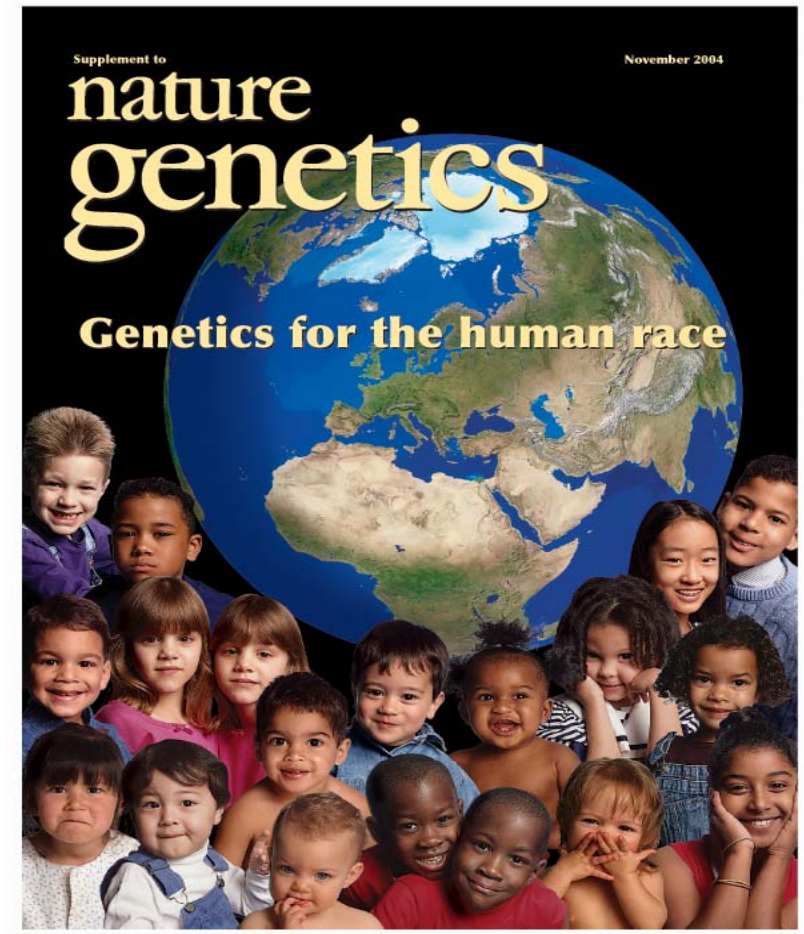
Can Genomics Help Heal The Schism Between Medicine And Public Health

Genomic Medicine and Health Disparities

Charles N. Rotimi, PhD
Professor and Director
National Human Genome Center
College of Medicine, Howard University

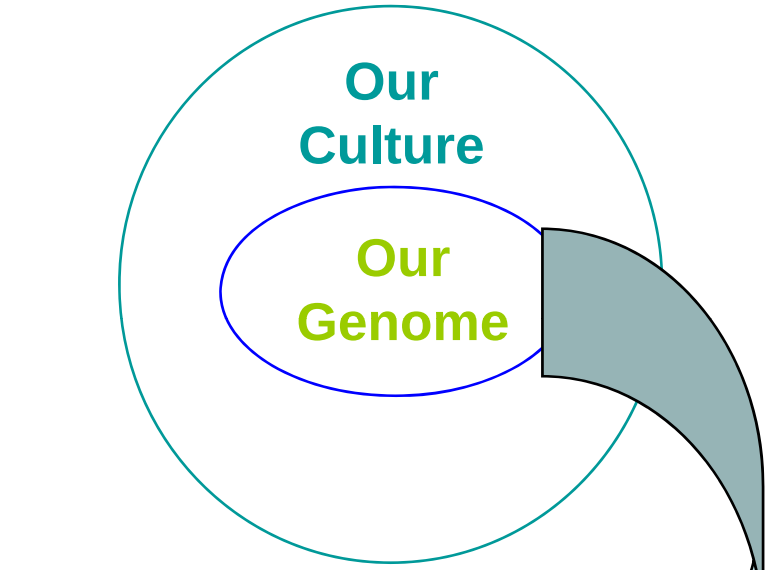
NIH\NCI monthly seminar 2007

We are similar and different



Our diversity is not an illusion.

Complex Interwoven History of Our Genome and our Culture



Who Are We?

How Are We Related?

Why ILL Health?

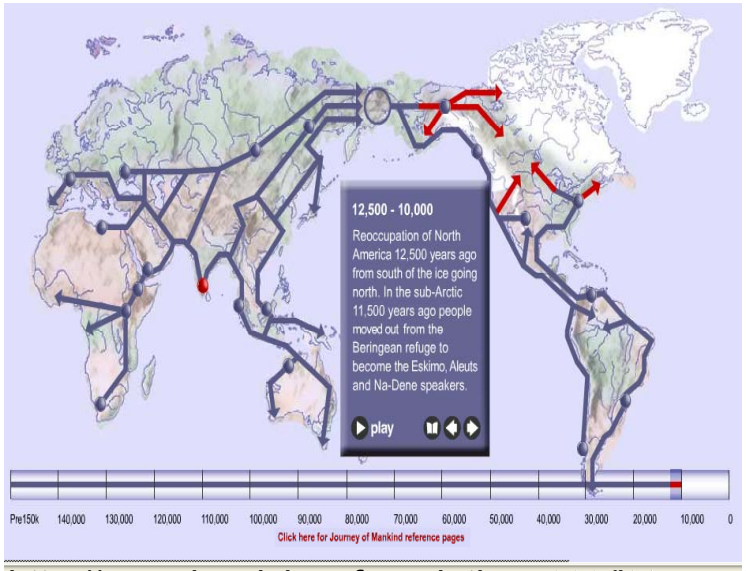
Why Differential Distribution of Diseases and Response to Drugs?

If we use genomic information correctly, we will simultaneously describe our similarities and differences without reaffirming old prejudices.

Also, depending on how we use this information, the potential exists to improve public health strategies across all human populations.

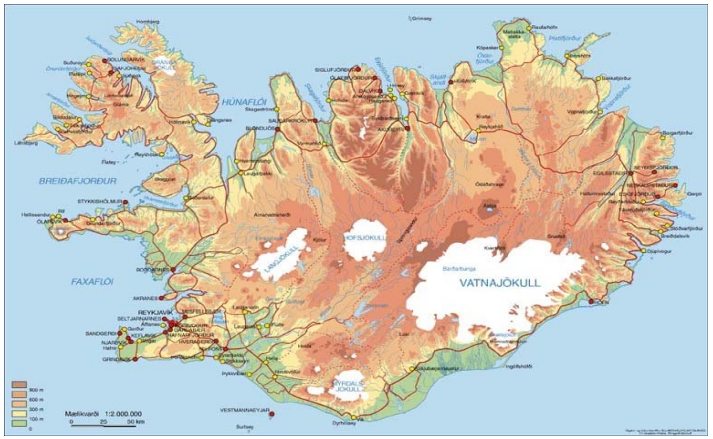
Genomics of Complex Diseases

The global effort to understand how our genetic background interact with our environment to increase susceptibility or resistance to complex diseases is forcing scientists to appreciate the complexity of human history.



http://www.bradshawfoundation.com/journey/

Complex disease research findings among the Icelandic people is proving to be just as informative for Africans and other world populations.



Why? Our recent shared history.

Genetic Basis of Human Diseases

Genetic factors contribute to virtually every human disease by way of increased

Susceptibility

Resistance

Affect severity or progression of disease and response to treatment.

Genetics in Public Health

Family History: a powerful public health tool

11% of families account for 86% of stroke

14% of families account for 72% of early Coronary Heart Disease and 48% of all CHD

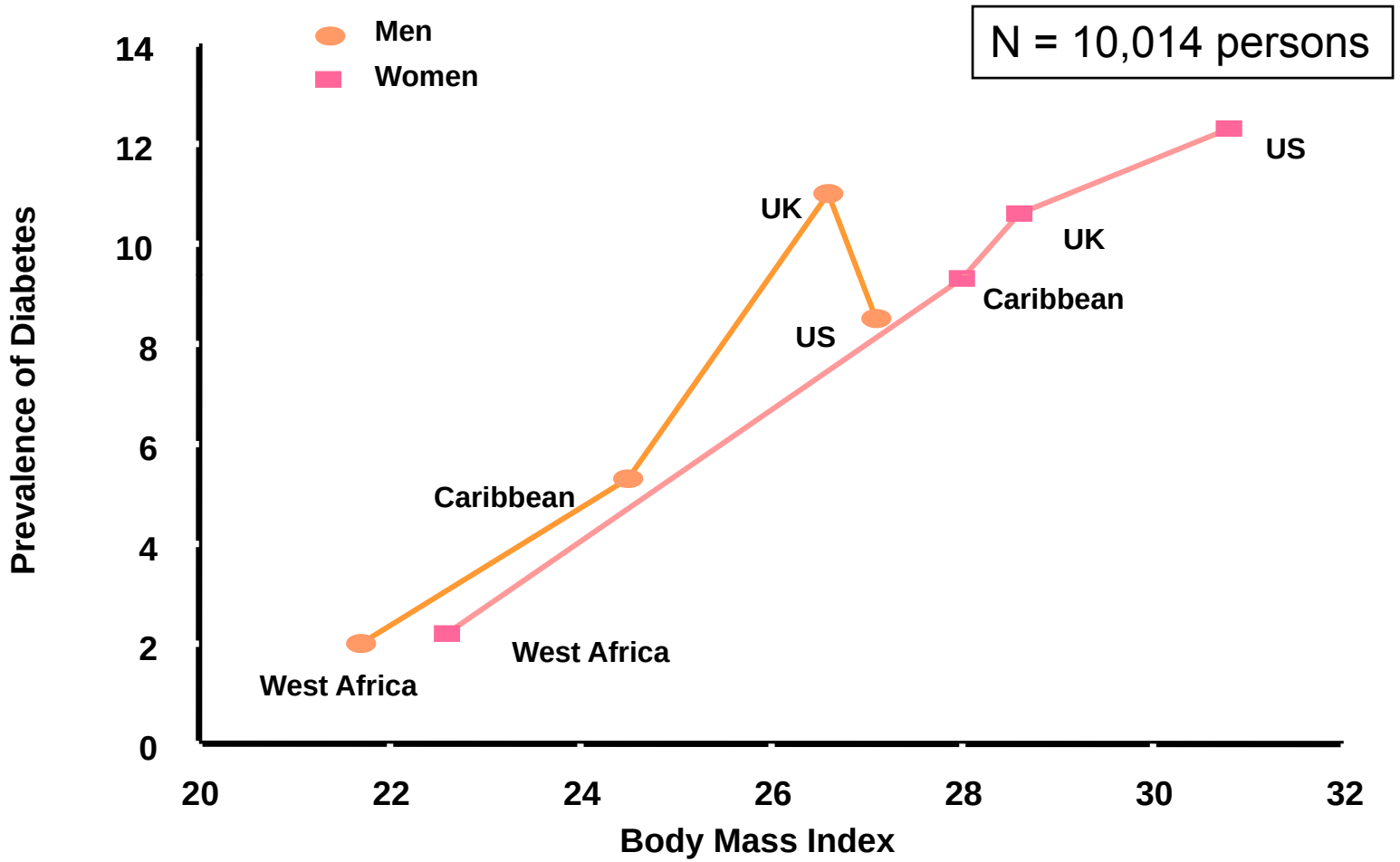
Disease frequency and the odds ratio comparing siblings of affected probands and siblings of unaffected probands.

		Relatives of Cases	Relatives of Controls	OR[1]	95% CI[2]
CHD	Yes	10	22		
	No	16	721	9.0	3.2,25.3
Hypertension	Yes	43	86		
	No	123	459	1.8	1.2,2.8
Stroke	Yes	2	10		
	No	16	716	7.3	1.2,44.8
Diabetes	Yes	9	34		
	No	31	644	3.3	1.3,8.2

[1] Odds ratio; Logistic model included age, gender and family size;[2] 95% confidence interval

Rotimi C. et al - Genetic Epidemiology 1994;11:397-407

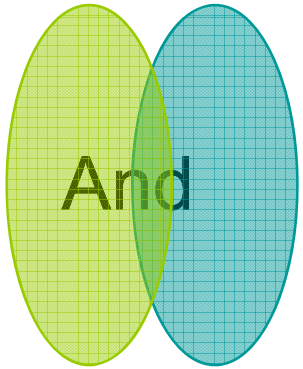
Prevalence of Diabetes by Mean BMI and Gender in Populations of the African Diaspora



Cooper R, Rotimi C, Kaufman JS, et al., Diabetes Care 1997

Human Diseases and Disparities in Health

Understanding Disease Etiology



Eliminating Health Disparity

Minority Health Disparities

Diseases, disorders, and conditions that disproportionately afflict individuals who are members of racial and ethnic minority groups

Other Health Disparity Populations

Population groups who suffer from health disparities when compared to the general population

HEALTH DISPARITIES OF CERTAIN CONDITIONS IN SELECTED POPULATIONS					
HEALTH CONDITION AND SPECIFIC EXAMPLE	INDEX IN SELECTED POPULATIONS				
	WHITE	AFRICAN AMERICAN	HISPANIC or LATINO	ASIAN or PACIFIC ISLANDER	AMERICAN INDIAN or ALASKA NATIVE
Infant mortality rate per 1000 live births[1]	5.9	13.9	5.8	5.1	9.1
Cancer mortality rate per 100,000[2]	199.3	255.1	123.7	124.2	129.3
Lung Cancer - age adjusted death rate[3]	38.3	46.0	13.6	17.2	25.1
Female Breast Cancer age adjusted death rate	18.7	26.1	12.1	9.8	10.3
Coronary Heart Disease mortality rate per 100,000[2]	206	252	145	123	126
Stroke mortality rate per 100,000	58	80	39	51	38
Diabetes diagnosed rate per 100,000	36	74	61	DSU	DSU
End-Stage Renal Disease rate per million[2]	218	873	DNA	344	589
AIDS – diagnosed rate per 100,000[4]					
Female	2	48	13	1	5
Male	14	109	43	9	19

http://ncmhd.nih.gov/our_programs/strategic/volumes.asp

Health Disparity and the Problem of “Race”

Health disparity is not new and is the result of multiple factors with deep roots in social, political and cultural practices.

It is not an American phenomenon but a global one. Some of the largest disparity in health occur among persons of similar ancestry living in the same continent.

Epidemiological data coming out of Africa, Central and South America are good examples.

Health Disparity

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

- Genomics (genetics) one piece of the puzzle.

Asthma Disparities – Genetic Explanation is Speculative and Confusing

In the United States, the number of asthma sufferers has more than doubled to an estimated 17.3 million in 1998 from 6.7 million in 1980 - CDC.

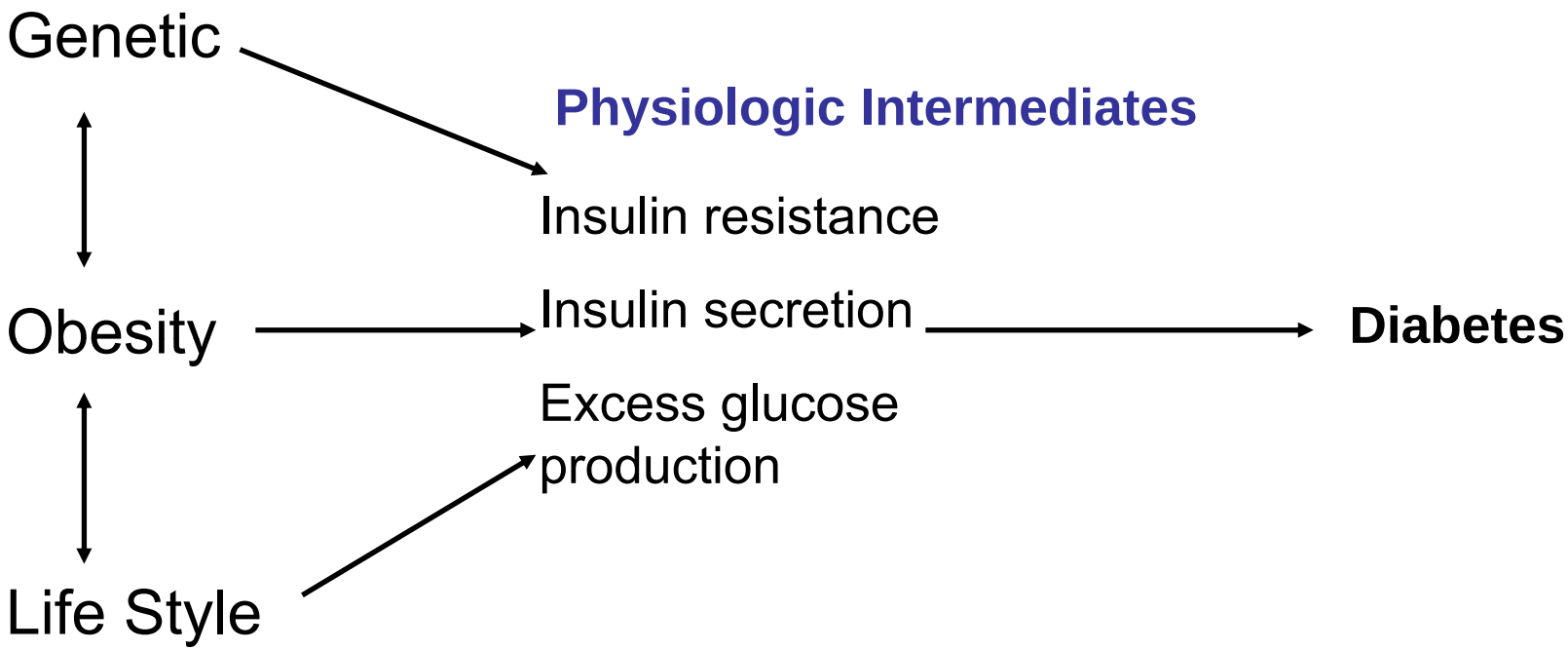
Experts say the increase is real. The epidemic cuts across racial and socioeconomic lines; white youngsters who live in suburbs are hardly exempt.

The prevalence of asthma is only slightly higher among blacks than whites, a difference that scientists suspect may be explained at least in part by genetics.

But when public health officials measure rates of hospital admissions, emergency room visits and deaths, they find that black and Hispanic patients, particularly those who are poor, shoulder a much heavier burden.

No one knows why the disparity is so great, but experts have some ideas. The poor tend to have less access to regular medical care, are less able to afford the medications they need and are more likely to be around environmental "triggers" that set off asthma attacks.

Complex Disease Research - Integrated Epidemiology



Genes alone are not enough: **Identical twins have identical genes but when one twin has T1D the risk for the other is ~ 50%. When one twin has T2D, the risk for other is ~ 75%.**

Environmental factors alone are also not enough: **Not all obesity or physically inactive persons have diabetes**

Genomics and Health Disparity

Working Examples

The CCR5 gene and HIV resistance

- The Genome organization of the chemokine receptors and HLA gene clusters and their influence on HIV/AIDS epidemic provides a major opportunities to understand the influence of pathogens on the evolution of the human genome

- A 32-bp deletion mutation in the coding region of the human *CCR5* gene is associated with resistance to HIV-1 infection

- Homozygotes are highly resistant to HIV-1 infection

- *CCR5*-Δ32 heterozygotes do not display a reduced risk for infection but do demonstrate a slower rate of disease progression after infection

- The *CCR5*-Δ32 allele is found almost exclusively in populations of European origin as well as populations that have undergone admixture with Europeans

Dean M et al. Annu Rev. Genomics Hum. Gen. 2002. 3:263-92

The *CCR5*-Δ32 allele is found at freq of 5%–15% in Caucasian; Rare or absent in African and Asian Populations

Examples from Europe

TABLE 3 *CCR5*-Δ*32* frequency in worldwide populations

Population	+/+	+/Δ	Δ/Δ	Sum	Freq. Δ-*32*
Europe					
Mordvinian	58	28	0	86	0.16
Iceland	75	24	3	102	0.15
Sweden	251	74	10	335	0.14
Slovakia	22	8	0	30	0.13
Estonia	116	42	0	158	0.13
Russian	141	43	2	186	0.13
Ashkenazi	721	209	19	949	0.13
Denmark	387	104	7	498	0.12
Britain	553	142	10	705	0.11
Lithuania	220	61	2	283	0.11
Poland	694	190	7	891	0.11
Finland	228	65	0	293	0.11
West Siberian	86	13	5	104	0.11
France-Brittany	79	20	1	100	0.11
Germany	168	45	1	214	0.11
France-North	1044	229	26	1299	0.11
Czech	434	109	4	547	0.11
Norway	79	21	0	100	0.11
US Caucasian	2677	460	26	2496	0.10
Netherlands	291	73	0	364	0.10

Examples from Africa

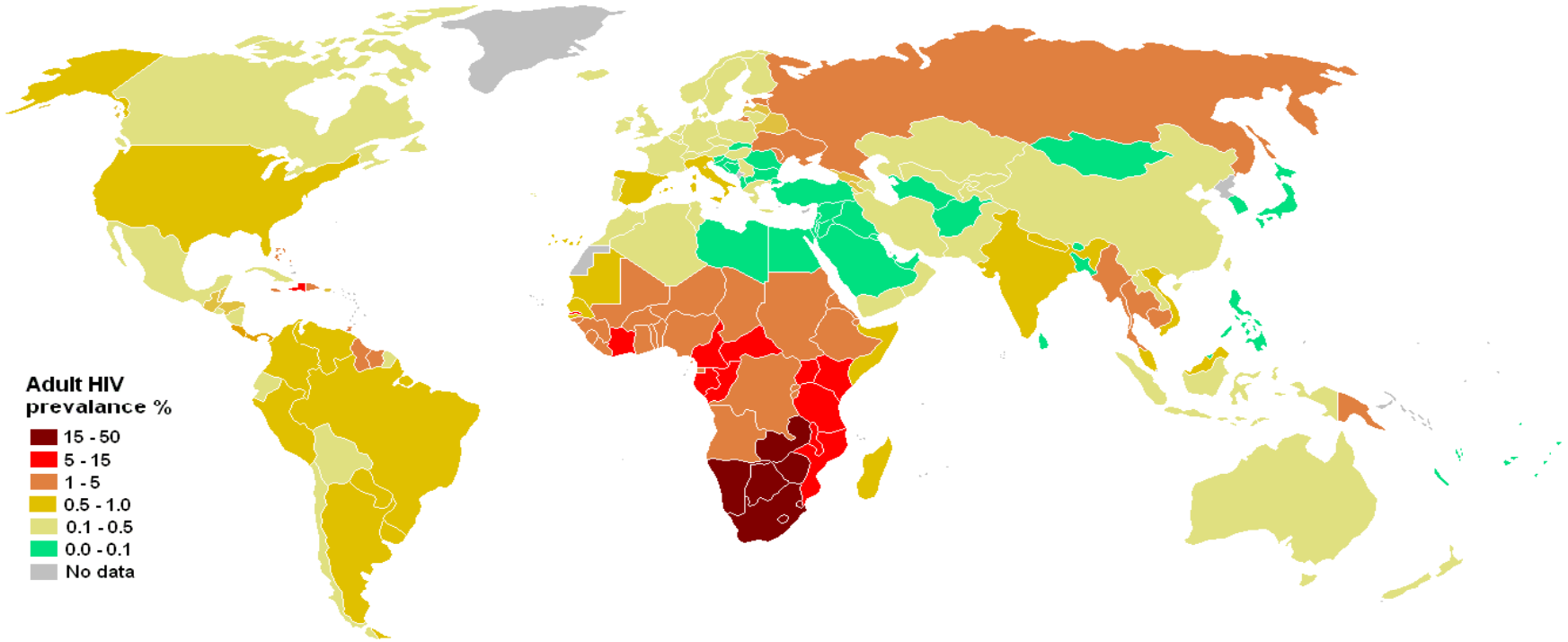
TABLE 3 (*Continued*)

Population	+/+	+/Δ	Δ/Δ	Sum	Freq. Δ-*32*
Morocco	163	3	1	167	0.01
West Africa	137	2	0	139	0.01
Nigeria	110	1	0	111	0.00
Gambia	103	0	0	103	0.00
Central African Republic	52	0	0	52	0.00
Kenya	87	0	0	87	0.00
Tanzania	7	0	0	7	0.00
Ivory Coast	87	0	0	87	0.00
Malawi	93	0	0	93	0.00
Zambia	96	0	0	96	0.00
Kalari San	36	0	0	36	0.00
Uganda	6	0	0	6	0.00
Madagascar-Merina	42	0	0	42	0.00
Madagascar-Bezanozano	16	0	0	16	0.00
Madagascar-Betsileo	42	0	0	42	0.00
Madagascar-Sihanaka	19	0	0	19	0.00
Africa	150	0	0	150	0.00
Africa-West, Central	124	0	0	124	0.00

Dean M et al. Annu Rev. Genomics Hum. Gen. 2002. 3:263-92

How much of this map is explained by the distribution of CCR5-Δ32 and similar variants?

Map of HIV prevalence worldwide



The plague *(Y. pestis)* is suspected to be the source of the CCR5 mutation selection. The European locale and timing of the major plague coincide with the calculated origin of the CCR5-Δ32 allele.

Functional SNP in the Promoter of SERPINH1 Gene and Increased Risk of Preterm Premature Rupture of Membranes

1. Preterm premature rupture of membranes is (PPROM) is the leading identifiable cause of preterm birth.
2. SERPINH1 (11q) encodes heat-shock protein 47 – a chaperone essential for collagen synthesis.
3. The SERPINH1 -656 minor T allele is more freq. in African populations & African Americans than European Americans (7.4% vs 4.1%).
4. The T allele displayed significantly reduced promoter activity compared to the major C allele in amnion fibroblasts, which lay down the fibrillar collagen that gives tensile strength to the amnion.
5. Case (244) and control (358) comparison showed highly significant association between -656 T allele and PPROM (OR=2.77; 95%CI: 1.73 – 4.95; Freq in cases=11.48%; Controls=4.47%).

Wang H et al. PNAS Sept 5, 2006

Functional SNP in the Promoter of SERPINH1 Gene and Increased Risk of Preterm Premature Rupture of Membranes

1. What is the nature of the association between SERPINH1variant and PPROM in European Americans?

2. Why is the freq of the disease-associated T allele so high in African Americans? Genetic drift or positive selection?

3. Sequence alignment to the chimpanzee and macaque genomes show the -656 C as the ancestral allele and that the T allele arose after the divergence of the primates.

4. If T allele is selectively disadvantageous in contemporary African Americans (PAR=12.3%), the expectation will be negative not positive selection or drift.

5. Speculation: Reduced fitness of -656 CT and TT genotype is a modern phenomenon due to increased human adult size and birth weight and that the T allele was selectively neutral for much of the evolution of the modern human lineage. If true, genetic drift may explain the increased T allele freq.

Taylor KH et al. PNAS Sept 5, 2006.

Leukotriene A4 Hydrolase Confers Ethnicity-Specific Risk For Myocardial Infarction

A haplotype (HapK) spanning the *LTA4H* gene encoding the leukotriene A4 hydrolase confers increased risks in both European and African Americans by up-regulating the leukotriene pathway.

Ethnicity	Freq of HapK - Controls	Relative Risks (RR)
European Americans	27%	1.16 (p=0.006)
African Americans	6%	3.57 (p=0.000022)
Africans (Nigerians)	Very rare	

African American Carriers of HapK, on average, had more European Ancestry (28.9%) compared to non carriers (19.8%; p=0.00008).
Conclusion: Occurrence of HapK in African Americans is due to European admixture. *Helgadottir A et al. Nature Genetics October 2005*

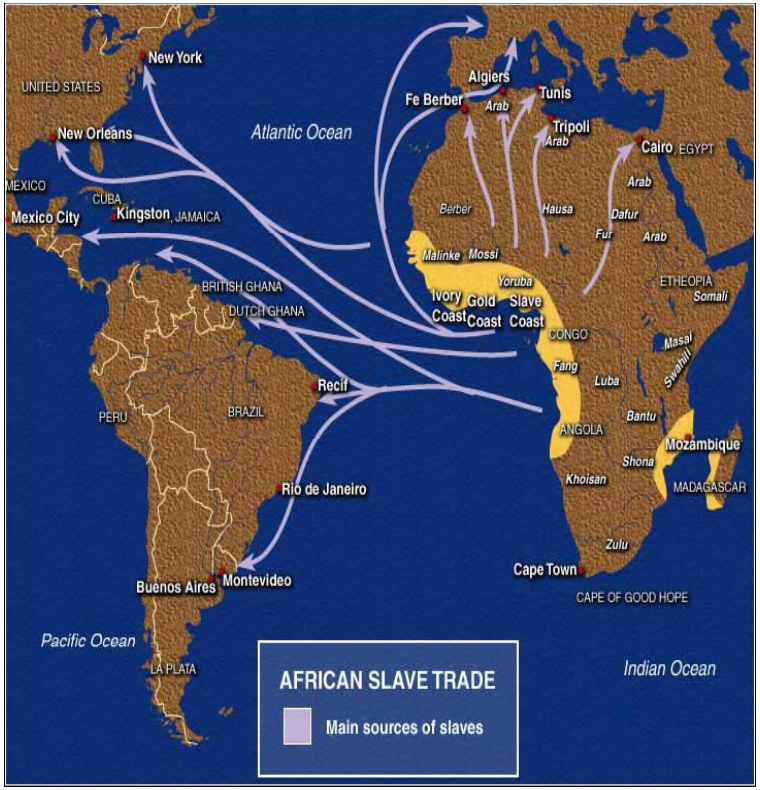
Proportion of European Ancestral

Populations	Proportion
Charleston, SC	11.6±1.3
Philadelphia	12.7±1.5
Baltimore	15.5±2.6
Detroit	16.3±2.7
Houston	16.9±1.5
Maywood, IL	18.8±1.4
New York	19.8±2.1
New Orleans	22.5±1.6
Jamaica	6.8±1.3

Used 9 autosomal DNA markers;
Para EJ. Am J Hum Genet 1998; 63:1839

Some African Americans may have as much as 40% or 70% Caucasian alleles, while others may have 5% or 10%.

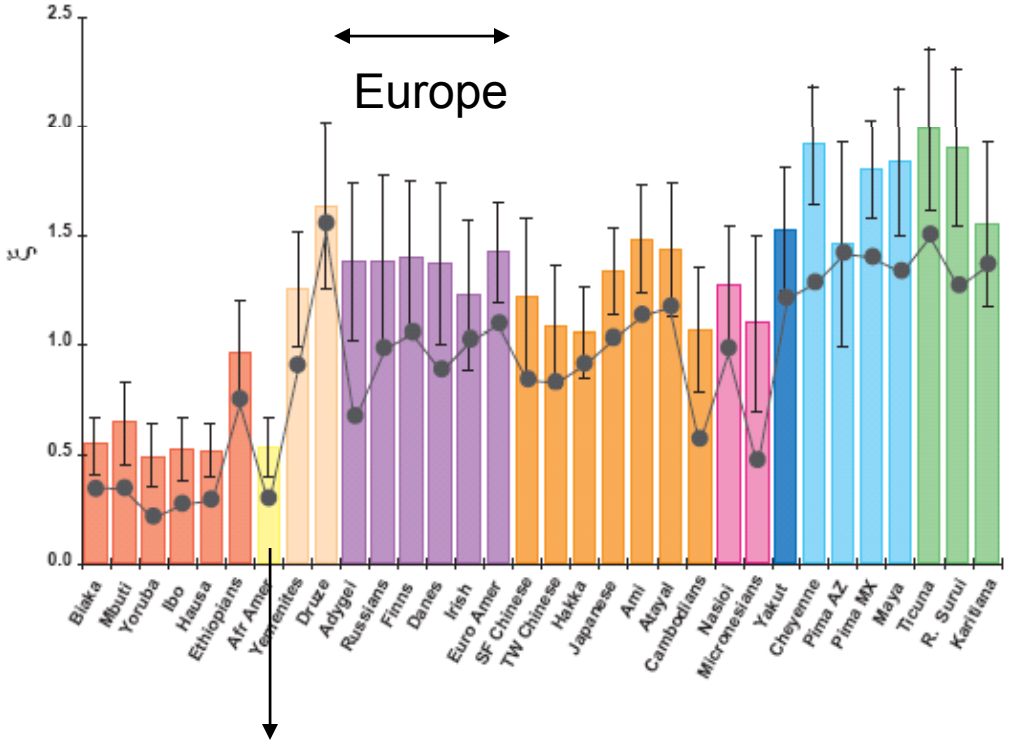
Nebert DW and Menon AG. Pharmacogenomics



Global Patterns of Genetic Variation

Implications for Study Design and genotyping/sequencing platforms

Average Linkage Disequilibrium (LD) for 83 SNPs across 21 haplotypes for 32 populations.



Af. Americans

Populations differ with respect to the organization of genetic variants along a chromosome.

Greater LD in Europe and Asia than in Africa and even greater LD in Native Americans.

Less heterozygosity and fewer population-specific alleles with increasing distance from Africa.

1. Gene-specific factors: Selection, Rates of mutation, Recombination
2. Demographic factors: population size & structure, founder effect and admixture)

(Tishkoff and Kidd. Nat Gen 2004).

A second generation human haplotype map of over 3.1 million SNPs

The International HapMap Consortium*

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

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

A second generation human haplotype map of over 3.1 million SNPs

The International HapMap Consortium*

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

Estimated Coverage of commercially available fixed arrays

Platform*	YRI		CEU		CHB+JPT	
	$r^2 \geq 0.8$ (%)	Mean maximum r^2	$r^2 \geq 0.8$ (%)	Mean maximum r^2	$r^2 \geq 0.8$ (%)	Mean maximum r^2
Affymetrix GeneChip 500K	46	0.66	68	0.81	67	0.80
Affymetrix SNP Array 6.0	66	0.80	82	0.90	81	0.89
Illumina HumanHap300	33	0.56	77	0.86	63	0.78
Illumina HumanHap550	55	0.73	88	0.92	83	0.89
Illumina HumanHap650Y	66	0.80	89	0.93	84	0.90
Perlegen 600K	47	0.68	92	0.94	84	0.90

* Assuming all SNPs on the product are informative and pass QC; in practice these numbers are overestimates.

Genomics and Society

Group Identity

Health Disparities

Human Genetic Variations

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†

Nature **449**, 913-918 (18 October 2007)

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

These and other published data show clearly that there are regional variations in the evolutionary forces that shaped the human genome.

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†

Nature **449**, 913-918 (18 October 2007)

Interpretation – “In the African samples (Yoruba in Ibadan, Nigeria), there is evidence of selection for two genes with well-documented biological links to the Lassa fever virus.”

PERSPECTIVE

Are medical and nonmedical uses of large-scale genomic markers conflating genetics and 'race'?

Charles N Rotimi *Nature Genetics* **36**, S43 - S47 (2004)

Sickle cell anemia is more frequently observed in people of African descent.

Also seen in a wide range of peoples around the world - Latinos, northwestern India and areas around the Mediterranean

It is not an “African” diseases, but a trait that evolved to confers resistance to malaria

Hence, it is found in people whose ancestry are from regions where malaria was once common (the Mediterranean, Arabia, Turkey, southern Asia and western and central Africa), but not southern Africa.

Ancestry, not race or ethnicity, is a better indicator of whether one carriers the markers of sickle cell.

The Medicalization of Race: Scientific Legitimization of a Flawed Social Construct.

Serious negative consequences of a physician's assumptions about a patient's race

Case 1: An 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.

Ritchie Witzig – Ann Int Med 1996;125:675-679

Serious negative consequences of a physician's assumptions about a patient's race --- Ritchie Witzig – Ann Int Med 1996;125:675-679

Case 2: A 24-year-old man, who was classified as black during the medical history, presented with progressive upper abdominal pain for 24 hours and was found to have a hematocrit of 0.22.

He stated that a doctor once told him he had "sickle cell," but he had never been hospitalized and had never needed treatment. The patient was admitted for management of sickle cell crisis, and two packed red blood cell units were transfused during the ensuing 24 hours.

The next morning, the patient had a witnessed cardiac arrest and was intubated immediately. During intubation, bright red blood was suctioned out of the pharynx and esophagus but oxygenation remained excellent.

The patient could not be resuscitated despite a 75-minute advanced cardiac life support effort.

His hematocrit at the time of the code was 0.13, and he had exsanguinated from a bleeding peptic ulcer. Sickle-cell trait or disease was not confirmed.

Pharmacogenomics

Pharmacogenomics

Low-hanging Fruit

Use our understanding of how individual genome modulates response to drug to optimize therapeutic strategies.

ONE SIZE DOES NOT FIT ALL

"Will Tomorrow Medicine work for all?"

Exacerbate Inequalities in the Provision of Health Care?

Pharmacogenomics
New Data – Old and Familiar Interpretation

- **The opportunity now exists to develop genetic tests that will allow physicians to tailor medicine to individuals and to groups defined by a collection of specific genetic variants**

- **Unfortunately, the new genomic information is being interpreted along old familiar social labels - race and ethnicity.**

- **Problem: There is considerable genetic variation both within and between socio-demographic groups.**

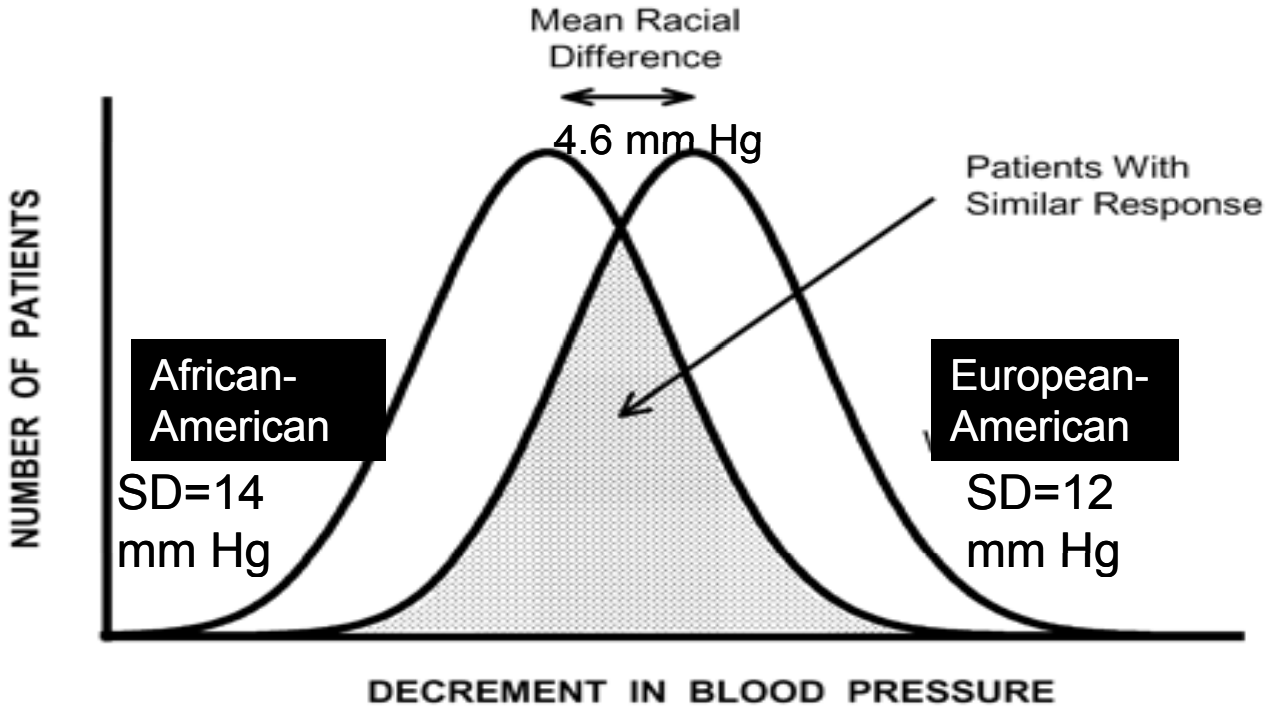
Pharmacogenomics: An Example

- N-acetyltransferase 2 (NAT2)
  - Enzyme involved in the detoxification of many carcinogens and the metabolism of many common drugs.
- NAT2 Variants
  - **Slow acetylators** Risk of toxicity
  - **Rapid acetylators**
- Slow acetylators
  - **14% East Asia**
  - **34% African Americans**
  - **54% Caucasians**

Anti-tuberculosis drug – isoniazid is inactivated by acetylation and the capacity of individuals to inactivate the drug is dependent on their genotype at the NAT2 locus

Blood pressure response to ACE inhibitors

(Sehgal, 2004, *Hypertension* 43: 566-72)



Similar drug-associated changes in diastolic BP was 90% for Calcium blockers; 81% for ACE

Conclusion: the majority of whites and blacks have similar responses to commonly used antihypertensive drugs. Clinical decisions to use a specific drug should be based on other considerations such as efficacy in individual patients, compelling indications, and cost.

The Misuse of Race in Medical Diagnosis

1. **Training of medical students in the act of assessing a patient – age, race, and gender (e.g., a 52-year-old white female; a 3-month-old Asian male; a 39-year-old Hispanic male). Actual identity of patient remains ignored.**

2. **Patients race by looking at them and not by asking**

3. **A childhood friend was not dx with cystic fibrosis until she was 8 years old because she was described over the years as a "2-year-old black female with fever and cough----- 4-year-old black girl with another pneumonia. Only when she was 8 did a radiologist, who had never seen her face to face, notice her chest radiograph and ask, "Who's the kid with CF?"**

4. **If by using a patient's ancestry in medical discourse we can narrow the range of possible dx, then at least we must be careful to describe accurately the genetic, ethnic, cultural, or geographical variables involved; guessing what category a person fits in is not acceptable.**

Richard S. Garcia, MD – *Pediatrics (2004) 1394-1395*

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.

The Challenge

Designing Studies to Understand Human Genetic Variation

The Use of ethnic/racial labels in Genomic studies is hindering the implementation of global systematic sampling needed to fully understand the scope of Human Genetic Variation and its impact on health, variable drug response and normal phenotypic variations

Geography Not Race

- Should geographic structure of genetic variation be considered during drug evaluation --Yes.
- Are racial labels sufficient to represent the geographic variation that is present? – No.
- *In the context of drug trials, there appears little justification for favouring socio-demographic labels over explicit genetic inference*
- What is needed is a comprehensive understanding of human genetic variation.

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."

Health Disparity

“The poor ranking of America’s black population in the indices of good health is a scandal of such long standing that it has lost the power to shock”

---The Lancet 1990 (a British journal)

Of all the forms of inequality, injustice in health is the most shocking and the most inhuman.

The Rev. Martin Luther King – Chicago, March 25, 1966