Genomics, Health and “Race”

Physician Assistant Competencies for Genomic Medicine
Where We Are Today and How to Prepare for the Future

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Overview

• Genomics, Health and “Race”
• Racialization of Disease: A Case Study
• Race Based Medicine: Genomics or Marketing?
• Populations: Categorizing People
• What are primary care physicians thinking?
• Human Genetic Variation
• Closing Thoughts
Grand Challenge

“Understand the relationship between genomics, race and ethnicity, and the consequences of uncovering these relationships”
Genomic Medicine offers the next major breakthrough in diagnosis, prevention, and cure of disease.
Should “race” be a part of genomic medicine?
NEW TWISTS ON DNA • 100 YEARS AFTER THE WRIGHT BROTHERS

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DOES RACE EXIST?

Science Has the Answer: Genetic Results May Surprise You

The Day the Earth Burned Reasons to Return to the Moon
Perspective

Medicine and the Racial

Elizabeth G. Phimister, Ph.D.

Policy Forum: Genetics

Toward a New Vocabulary of Human Genetic Variation

Sounding Board

Race and Genomics

Howard S. Cooper, M.D., Jay S. Kaufman, Ph.D., and Ryesan J. Parker

Genetic Structure of Human Populations


We studied human population structure using genotypes at 377 microsatellite loci in 1056 individuals from 52 populations. Within-difference among individuals account for 23 to 25% of genetic variation.

Commentary

The Importance of Race and Ethnic Background in Biomedical Research and Clinical Practice

Ruben Gonzalez Burchard, M.D., Elad Ziv, M.D., Natasha Coyle, Ph.D., Scarlett Lin Gomez, Ph.D.

Race, Ethnicity, and Genomics: Social Classifications as Proxies of Biological Heterogeneity
DECONSTRUCTING THE RELATIONSHIP BETWEEN GENETICS AND RACE

Michael Bamshad®, Stephen Wooling®, Benjamin A. Salisbury® and J. Claiborne Stephens®

The success of many strategies for finding genetic variants that underlie complex traits depends on how genetic variation is distributed among human populations. This realization has intensified the investigation of genetic differences among groups, which are often defined by convenience.

Genetics, race, ethnicity, and health

Neil Pearce, Sunia Foliaki, Andrew Sporle, Chris Cunningham

Genetics plays only a small part in ethnic differences in health, and other factors are often more amenable to change.
Pharmacogenetics and geographical ancestry: implications for drug development and global health

Racial Differences in the Use of BRCA1/2 Testing Among Women With a Family History of Breast or Ovarian Cancer

The Practitioner's Dilemma: Can We Use a Patient's Race To Predict Genetics, Ancestry, and the Expected Outcomes of Treatment?

Patients' Attitudes Toward Health Care Providers Collecting Information About Their Race and Ethnicity

A common nonsense mutation in EphB2 is associated with prostate cancer risk in African American men with a positive family history

SIDS: genetic and environmental influences may cause arrhythmia in this silent killer

Should ethnicity serve as the basis for clinical trial design?

BiDil raises questions about race as a marker

Approval of ‘race-based’ drug is stimulating efforts to detect and predict true subgroups for drug response
DNA Testing: In Our Blood
By Claudia Kalb

It is connecting lost cousins and giving families surprising glimpses into their pasts.
Newsweek - Feb. 6, 2006 issue

Race May Be Factor In Lung Cancer Greater Risk Found For Blacks Who Smoke
By Rob Stein
Washington Post Staff Writer
Thursday, January 26, 2006;

This racist undercurrent in the tide of genetic research
As taboos fall away, there’s a danger that denial of racial difference will be replaced with uncritical acceptance
Marek Kohn
The Guardian
January 17, 2006

Doctor’s Guide News
Race/Ethnicity Is Predictor for Some HIV-1 Therapy
AMHERST, MA -- January 24, 2006
Researchers from the University of Massachusetts Amherst and the University of Pennsylvania have shown that race/ethnicity is a predictor for some patients with HIV-1 on HAART (highly active antiretroviral therapy).

The NEW ENGLAND JOURNAL of MEDICINE
Dissecting Racial and Ethnic Differences
Neil Risch, Ph.D.
N ENGL J MED 354:4  WWW.NEJM.ORG  JANUARY 26, 2006

LRRK2 G2019S as a Cause of Parkinson’s Disease in North African Arabs

LRRK2 G2019S as a Cause of Parkinson’s Disease in Ashkenazi Jews
Racial disparity in the frequency of recurrence of preterm birth
Zachary A.-F. Kistka; Lisanne Palomar; Kirstin A. Lee, MD; Sarah E. Boslaugh, PhD; Michael F. Wangler, MD; F. Sessions Cole, MD; Michael R. DeBaun, MD, MPH; Louis J. Muglia, MD, PhD

Nature Genetics 39, 226 - 231 (01 Feb 2007)

Common genetic variants account for differences in gene expression among ethnic groups
Richard S Spielman1, Laurel A Bastone2, Joshua T Burdick3, Michael Morley3, Warren J Ewens4 & Vivian G Cheung1,3,5

Nature Genetics 38, 652 - 658 (01 Jun 2006)

A common variant associated with prostate cancer in European and African populations

Nature Genetics 38, 68 - 74 (01 Jan 2006)

A variant of the gene encoding leukotriene A4 hydrolase confers ethnicity-specific risk of myocardial infarction
“Race is biologically meaningless…”

“…Instruction in medical genetics should emphasize the fallacy of race as a scientific concept and the dangers inherent in practicing race-based medicine.”

“There is great validity in racial/ethnic self-categorizations, both from the research and public policy points of view.”

Do we inappropriately racialize disease?
Incurable ‘Negro Disease’ Strikes Five in Family

Problems linked to sickle cell anemia cloud life in upper New York home

Most parents expect to encounter a fair share of problems as well as pleasure in the rearing of their children, but fate has weighted the scales heavily on the negative side for Hampp Johnson and his wife, Alice, of Saratoga Springs, N. Y.

Through ten years of hardship and deprivation, they have looked on helplessly while two of their six children have wasted away from the debilitating effects of sickle cell anemia, an incurable, hereditary blood disease predominant in Negro youths. Then, too, they are constantly plagued by the thought that more of the family will also develop the disease.

Medical bills accumulated during recurring periods when the children were ill have left them heavily in debt, and they are shunned by many neighbors who do not realize that the disease is not contagious.

Their only comfort is in knowing that they are far from being alone in this unfortunate situation. Sickle cell anemia is more common in some parts of the country than all other primary blood diseases put together, including leukemia, hemophilia and platelet diseases. It is believed to cause more paralysis than polio, can affect any organ of the body and is a major cause of maternal mortality. Though it has been found occasionally in whites of the Mediterranean type, approximately eight to nine per cent of the Negro population carries the benign sickle cell trait, while the disease, fortunately, occurs much less frequently—about one out of every 400 American Negroes. Causes by presence of the abnormal hemoglobin S in the red blood cells, which results in fluids collapsing and assuming a crescent or sickle shape, sickle cell anemia usually manifest in its victims before they reach the age of four. Then, they might become pale, listless, have a fever and complain of abdominal, thoracic and particularly skeletal pain. Crises, or periods of extreme illness, are followed by remissions when the victims appear to be fairly well. But they remain highly susceptible to infection and serious conditions like pneumonia and tuberculosis, which frequently result in early death.

These are the grim truths that haunt the Johnson family. There is a story that could be duplicated in hundreds of other homes throughout the country.

Marleen Ann Johnson, 12, was first stricken when she was three years old. Within a few days, Perry Lee Johnson, her older brother by one year, also fell ill. At first their condition were diagnosed as leukemia, and Marleen was given only months to live. But subsequently, doctors...
“The most significant feature of sickle cell anemia is the fact that it is apparently the only known disease that is completely confined to a single race”

Annon, Sickle Cell Anemia: A Race Specific Disease. JAMA 1947; 133:33
Science Times
The New York Times

Study Points to Genetics in Disparities in Preterm Births

BY NICHOLAS BAKALAR

Black women have significantly higher rates of preterm birth than white women, and a new study suggests there may be underlying genetic factors even when other known risks are taken into account.

The researchers, who published their findings this month in The American Journal of Obstetrics & Gynecology, say that even though preterm birth is not a desirable outcome, it may provide some advantage, perhaps protection against diseases — in somewhat the same way the gene for sickle cell confers protection against malaria.

“We have to think of everything in the context of what’s been evolutionarily advantageous,” said Dr. Lewis J. Muguia, a professor of pediatrics at Washington University in St. Louis, who was the senior author of the study.

Dr. Muguia noted that during a normal pregnancy, certain immune responses are suppressed, and that cytokines, the molecules involved in healthy immune response, are heavily involved in preterm birth.

“The same things that select for a robust immune response,” he said, “may also confer a risk for giving birth early.”

Some experts remain skeptical. Neil J. Risch, director of the Institute for Human Genetics at the University of California, San Francisco, said he was not impressed with the quality of the evidence.

“They’re inferring something is genetic by elimination of other factors,” he said. “But geneticists believe that to implicate something as genetic requires direct evidence, as opposed to evidence by absence. One should use high standards of evidence before trying to directly implicate genetics in group differences. There could be a genetic contribution, but they haven’t shown it.”

That black women give birth prematurely more often than white women has been demonstrated in numerous studies, and there is wide agreement on many of the risks. The mother’s age, prenatal care, socioeconomic status, education level, body mass index, smoking and gestational diabetes have all been shown to affect the likelihood of preterm birth.

But the new study found that black women still had higher rates of preterm birth even after accounting for all these variables.

The researchers used the Missouri Department of Health and Senior Services’ database of more than 71,000 live births from 1989 to 1997. They found that compared with white women, black women were twice as likely to give birth from 20 to 24 weeks; that their rate of overall preterm birth is higher; and that the median time for recurrence is two weeks earlier — 21 weeks for black mothers, compared with 23 for whites. (Normal gestation is 37 to 41 weeks.)

The researchers found that race was an even more powerful predictor than lack of prenatal care, which is itself one of the strongest risk factors for prematurity. For black women, the risk of recurrent preterm delivery is four times as great as it is for white women.

The study also found that for both blacks and whites, the most likely time for the birth of a second preterm child is the same week as the first preterm delivery. These findings suggest, but do not prove, that there is a genetic contribution to prematurity birth.

A co-author of the paper, Dr. F. Sessions Cole, also a professor of pediatrics at Washington University, acknowledged that the study was not a genetic analysis. But he said that should be the next step.

“There is no specific candidate gene or pathway identified here,” Dr. Cole said. “But this is a sufficiently large and robust cohort that differences in genetic contribution can be made. The study provides momentum for a genomic approach to understanding the racial disparity between blacks and whites in rates of prematurity.”

Dr. Muguia acknowledges that because many people are genetically mixed, critics say it is impossible to associate race with any specific gene. But he added, “There have been enough studies to show that when you look at people’s self-reported race, it does track with specific markers of ethnicity.”

Previous studies have shown that the tendency to give birth prematurely is inherited, and that women who were themselves born prematurely are significantly more likely to give birth to preterm infants. One study found that women born at 36 weeks of gestation or less are more than twice as likely as women born after 36 weeks to have their own babies prematurely.

Dr. Muguia said that gene and environment interact. “There are likely genetic variations that will require certain environmental exposures to result in preterm birth,” he said, “and these environmental contributors vary as a function of race as well. This complicates the overall analysis of something so complex.”

Dr. Jerome F. Strauss, dean of the Virginia Commonwealth University School of Medicine, said that the findings were “weak and significant” and that “they add support to the idea that genetic factors contribute to the disparity between African-Americans and Americans of European descent in rates of prematurity.”

Dr. Strauss was not involved in the study.

Although no one has identified a specific gene for prematurity, Dr. Strauss and his colleagues have identified a gene variant, much more common in people of African descent, that confers an increased risk of preterm rupture of the fetal membranes. Still, Dr. Muguia said, even that finding gives no indication of the overall contribution of genetics to the likelihood of giving birth prematurely.

The authors emphasize that their analysis does not prove that the disparity in preterm births has a genetic component, because unknown variables that go along with black race may also contribute.

“Many people feel they’ve done something wrong if they have a preterm infant,” Dr. Muguia said. “But there are still other risk factors that aren’t in their control, like their genetic make-up, that we need to know more about — for both whites and blacks.”

TUESDAY, FEBRUARY 27, 2007

A girl who was born at 27 weeks being fed through a tube.
Should “race” be part of the equation in clinical decision-making?
SCIENTIFIC AMERICAN

Will you get sick?
Antibodies could foretell the future of your health

Predicting Disease
How do health professionals use race and ethnicity?

• “There’s a difference between race and ethnicity. And that’s an important distinction. There are an awful lot of ethnic distinctions. I’m much more concerned about basal cell carcinoma since somebody who has been a sunbather who happens to be from Ireland than I am from somebody who is from Kenya. And that may not be a racial question. It may be ethnicity. Every patient I see initially gets the full family history so I know where their parents are from.” (White physician from Baltimore)
A model for understanding the role of race and genetics in clinical decision making
Should drugs be targeted to OMB racial and ethnic groups?
FDA Approves BiDil for the Treatment of Heart Failure in Black Patients
Indications And Usage

“BiDil is indicated for the treatment of heart failure as an adjunct to standard therapy in self-identified black patients to improve survival to prolong time to hospitalization for heart failure, and to improve patient reported functional status.”
Who is self-identified Black?
Historical Analysis Demonstrates That the United States’ Definitions of Race Have Been Fluid, Inconsistent, and Often Influenced by Social and Political Factors
U.S. Census Definitions of Race

1790 - Free (White or Other), Slave
1860 - White, Black, Mulatto
1890 - White, Black, Mulatto, Chinese,
      Indian, Quadroon, Octoroon,
      Japanese
1900 - White, Black (of Negro Descent),
      Chinese, Indian, Japanese
African Ancestry

Northern European Ancestry

Asian Ancestry

Pacific Islander Ancestry

American Indian Ancestry

Hispanic/Latino Ancestry
Race Based Medicine: Genomics or Marketing?
New Pathways For Market Development
Effective Direct-to-Ethnic Physician, Direct-to-Multicultural Consumer and Direct-to-Community Strategies...

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Results: General Attitudes about Race-Based Therapies

• “Unless you’re going to show me that the African American enzyme for xyz is shaped or works differently that some other race, that makes no sense to approach it from that perspective.”

African American physician from Detroit
Results: General Attitudes about Race-Based Therapies

• “I think we need to know the genetics because…there’s a lot of crossover racially. And I think we need to know the genetics because I may have some gene that makes me work better for this drug than that drug. And why shouldn’t I get that drug because my skin is white if it’s made for blacks? Why shouldn’t I be able to be tested to see if I have that gene to see if I would benefit from that drug?”

White physician from Detroit
Results: General Attitudes about Race-Based Therapies

• “I can’t see were there’s an advantage to identifying the differences between the different races versus the non-different races when you are coming to find these differences. I think it’s just as important to know the difference between two white people’s genetic makeup in terms of drug response as it is to know the difference between a white person and a black person.”

White physician from Baltimore
Results: Attitudes about ACE-Inhibitors

• “I didn’t say I won’t use ACE-inhibitors in a black population. I use it on every patient with proteinuria. I will not deny a black patient an ACE. But at the molecular level, there is a response that is muted compared to Caucasians.”

White physician from L.A.
Results: Medical and Social Implications

“What I don’t want to happen is that race is used as an excuse for why there are differences or disparities. Well there’s more Blacks in renal failure because they have uncontrolled hypertension because they are made up that way which allows us to dismiss all of the environmental issues…That’s my fear with the way we are moving toward the development of race-specific drugs.”

African American physician from Atlanta
Human Genetic Variation
African origin of anatomically modern humans

adapted from Hedges, 2000, Nature 408: 652-3
How is variation distributed within and between populations?

Average difference between individuals *between* major populations

Average difference between individuals *within* major populations
Ancestry vs. Race

“European”

“African”

“African-American”

Native American

“European”

“African”

“African-American”

L. Jorde
Understanding Human Genetic Variation Race and Ethnicity

• Large numbers of DNA polymorphisms can inform us about ancestry and population history
• Responses to many therapeutic drugs involve variation at just one or a few genes (along with environmental variation)
• These variants typically differ between populations only in their frequency
Understanding Human Genetic Variation Race and Ethnicity

- Because of a recent origin and subsequent gene flow, humans are genetically similar.
- Genetic variation is correlated with geography and tends to be distributed continuously across geographic space.
- "Self Identified Race" correlates with human genetic variation, but it is an imprecise correlation; ancestry is more informative.
- Personalized medicine, will be medically more useful than ethnicity or race.
Should Medicine Be Color Blind?

Better Question:

When should we use race and ethnicity to assist with personalized health care decisions?
Closing Thoughts

• There is limited empirical data on health professionals understanding and beliefs about race and human genetic variation

• Thoughtful use of racial and ethnic categories is required in health services, clinical and genetic research and clinical care
7. Random mutations cause all of the genetic variation in the human genome.

false  ○  ○  ○  ○

8. The variation in the human genome includes both disease causing gene variants and variants that have no effect on health and disease.

false  ○  ○  ○  ○
Next Steps

• Developing a deeper understanding of health professionals’ knowledge of human genetic variation and health professionals’ attitudes about human genetic variation, and use of race in clinical practice will be instrumental for successfully translating genomics into clinical practice.
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