Discovering the Full Spectrum of Cardiovascular Disease
Minority Health Summit 2003
Report of the Basic Science Writing Group

Ivor J. Benjamin, MD; Donna K. Arnett, PhD; Joseph Loscalzo, MD, PhD

Despite considerable overall improvement in the clinical prevalence and outcome of cardiovascular disease in the US population during the past 50 years, striking disparities in disease burden plague specific racial/ethnic subgroups. Black patients with cardiovascular disease (CVD) in particular have increased morbidity and mortality as compared with white patients. For example, a black man between 45 and 65 years old is 4 times more likely to have a stroke than his white counterpart. Even when accounting for access to high-quality health care, ethnic minorities bear a higher burden of obesity, type 2 diabetes mellitus, and hypertension as compared with whites. The mechanisms for these disparities remain incompletely understood but likely include a combination of genetic, environmental, and socioeconomic factors. If recent advances in basic science are to be exploited to reduce disparities in cardiovascular health care, then the emerging advances in basic science are likely to afford us unprecedented opportunities for deciphering the complex mechanisms involving race/ethnicity, genetic differentiation, allele frequency disparities, and gene–environment interactions.

When Do Genetic or Other Differences That Take Into Account Race and Ethnicity Apply to the Study of Disparities in Health Care?

The completion of the draft sequence derived from the Human Genome Project provides the scientific framework for understanding the genetic basis for similarities or differences between population groups. On the basis of the evidence to date, the Human Genome Project suggests that racial classification may not be useful for biomedical research because genetic variation is a continuous phenomenon that does not lend itself to clear boundaries among population groups. Indeed, disparities in genomic variation most likely are surrogates of the ethnohistory of the major continental groups. Because race and ethnicity historically have been used as social instruments for subjugation and discrimination, the contextual framework for racial classification in biomedical research will likely remain controversial and highly scrutinized, especially in the United States.

Thanks to the Human Genome Project, the handful of genes that control physical appearance has perhaps minimized the issue of race in the genetic code while refuting a plausible biological basis for “racial” subgroups. Without doubt, the most frequent uses of racial and ethnic categories in fields such as clinical and epidemiological research are pivotal for pursuing hypothesis-driven studies on gene–environment interactions. In turn, the results gleaned from such studies could have bidirectional outcomes to guide clinical decisions, as well as to generate new hypotheses in basic research, a discipline more suited to mechanistic questions. On the basis of the available evidence, the present writing group strongly supports the position taken by others who have advocated that the benefits gained for society and the scientific community from the collection of data on race and ethnicity outweigh the potential risks.

What Are the Implications of Genetic Differentiation on Race and Ethnicity?

Population geneticists have shown that although the genetic variation between specific population groups is smaller than within population groups, the amount of variation in the human genome is substantial. At least 15 million genetic polymorphisms are estimated to exist in the human genome. Analysis of polymorphisms in the 5 racial/ethnic groups identified in the 2000 US Census show that these 45 groups aggregate genetically. The allele frequencies for single-nucleotide polymorphisms and microsatellite markers indicate a...
median difference of 15% to 20% between racial and ethnic groups; 10% of polymorphic markers differ by ≥40%. Although now a unifying sequence defines racial groups, the variation within the human genome does appear to align along self-identified race or ethnicity. Thus, the frequency of alleles associated with CVD is likely to vary substantially among racial/ethnic groups.

What Is the Scientific Evidence for a Genetic Basis for Disparities in Cardiovascular Health Among Racial/Ethnic Groups?

Evidence has been uncovered that risk alleles for a variety of cardiovascular risk factors are more common in some racial/ethnic groups than they are in others. For example, the factor V Leiden mutation, which is associated with thromboembolic diseases, occurs in 5% of white populations but is found in <1% of East Asian or black populations. Alleles within candidate genes for disease-causing genes, in particular sodium-sensitive forms of hypertension, are more common in blacks than in whites. In addition to these specific examples, allele frequency disparities between racial and ethnic groups have been reported for genes that contribute to many cardiovascular risk factors and drug metabolism. In addition to allele frequency disparities between racial and ethnic groups, environmental factors that differ between groups also may play a role in disease pathogenesis. Gene–gene interactions, or epistasis, also is likely to contribute to the disparities in CVD observed between racial and ethnic groups. One cautionary note is that the predictive value of genetic variants may change substantially in different populations and among people in the same ethnic groups. For example, people with hypertension with a C825T polymorphism of the gene encoding the G protein γ3-subunit, which regulates cell growth, were shown to have a greater risk of developing LVH. Without doubt, therapies should aim to eliminate reversible conditions. Recent trials suggest that treatments targeting the renin-angiotensin system are especially successful in the regression of LVH.

In young adults, a family history of essential hypertension imparts a stronger risk factor for higher systolic blood pressure and left ventricular mass than a similar family history of myocardial infarction to either systolic blood pressure or a history of myocardial infarction. These findings might have important implications for diagnosis and early therapeutic interventions, before deleterious cardiac manifestations become irreversible, perhaps even at the time of clinical presentation.

In the Study of Left Ventricular Dysfunction Trial, clinical responders for improved ventricular ejection fraction and reduced rate of hospitalization after treatment for 3 years with enalapril, the angiotensin-converting enzyme inhibitor, were significantly greater in whites as compared with blacks, suggesting that either race is a surrogate for disease outcome or inadequate dosing in undefined genetic variants may influence drug metabolism. Substantial evidence exists that genetic variants in the cytochrome P450 enzymes, for example, account for disparities in drug metabolism among individuals, especially among racial or ethnic groups.

The emerging discipline of pharmacogenetics, which addresses how genes (alone or in combination) affect drug response, can conceivably provide biological insight into an
array of existing deficiencies in predicting adverse drug responsiveness and nonresponsiveness. From a biological context, a comprehensive list of candidate genes, based on sequence variation (eg, single-nucleotide polymorphisms), may provide investigators with the tools to explore the mechanisms of drug toxicity and predisposing factors that determine disease susceptibility. Beyond the imprecision of skin color or ethnicity, biological determinants are likely to provide opportunities for rational drug design based on molecular modeling of gene variants, as well as to enhance clinical decision making for therapies that are tailored to specific diseases. Of interest, it is conceivable that during the development and implementation of marketing and educational strategies aimed to reduce disparities in health care, important dividends will be derived, especially when sensitivity to race and ethnicity are appropriately addressed.

Although beyond the scope of this article, diabetes and obesity are important risk factors for ventricular remodeling, which accompanies the onset of ventricular dysfunction and heart failure. Genetic determinants, these risk phenotypes, and their biological variants between and within ethnic and racial groups currently are being studied.

Vascular Biology: How Does It Vary in Ethnic Minorities?

Difference in vascular function, especially with the bioavailability of nitric oxide, has been proposed as a mechanism to account for these ethnic disparities in CVD outcome. Several groups have reported impaired vascular function in healthy and hypertensive blacks as compared with whites.19–21 This impairment is likely to be important in that it may reflect a deficiency of bioactive endothelial nitric oxide that compromises its actions as a mediator of vascular homeostasis, including vasodilation, platelet inhibition, smooth muscle cell growth inhibition, and antiinflammatory function.

Decreased nitric oxide bioactivity can arise from impaired production, enhanced oxidative inactivation, or both. Polymorphisms in the endothelial nitric oxide synthase gene have been identified that alter nitric oxide production. One of these, the 4a/4b polymorphism, is generated by a variable number of tandem repeats in intron 4; of note, the 4a variant is more common among blacks than it is among whites and is associated with a decrease in the expression of endothelial nitric oxide synthase and a resulting decrease in nitric oxide production.22,23 A recent study showed that homozygosity for the 4a polymorphism conferred a significantly increased risk of myocardial infarction before age 45 in blacks.24

Another important genetic determinant of nitric oxide synthesis and its oxidative inactivation is glucose-6-phosphate dehydrogenase (G6PD). A deficiency of G6PD is the most common enzymopathy globally, and it is particularly common in the US black population (≈11% to 15% prevalence). Until recently, G6PD deficiency was believed to be important only with regard to protecting erythrocytes from oxidative stress and hemolysis. Recent work has shown, however, that G6PD deficiency is a key determinant of vascular function and that its deficiency can lead to impaired nitric oxide production and enhanced vascular oxidant stress. As the principal endothelial source of NADPH, G6PD regulates the availability of this endothelial nitric oxide synthase cofactor, as well as 2 cofactors (tetrahydrobiopterin and glutathione) the synthesis of which depends on NADPH. In addition, and importantly, limiting NADPH synthesis impairs glutathione disulfide reduction to glutathione by glutathione reductase, which in turn limits the antioxidant activity of glutathione peroxidase, increases oxidant stress, and promotes oxidative inactivation of nitric oxide. Leopold and coworkers25,26 have demonstrated these principles in cultured endothelial cells, as well as in an animal model of G6PD deficiency. Of equal importance, these investigators recently showed that healthy black subjects with G6PD deficiency have impaired endothelium-dependent vasodilation and increased oxidant stress as compared with age-matched controls.

The consequences of the vascular oxidant stress and impaired nitric oxide bioavailability of G6PD deficiency are potentiated in ischemia. Isolated hearts from mice that are deficient in G6PD have abnormal functional responses to ischemia reperfusion, with increased left ventricular end-diastolic pressure and decreased developed pressure.27 In addition, endothelial proliferation and angiogenic responses in vitro and in vivo are blunted by G6PD deficiency as a consequence of both impaired nitric oxide bioavailability and decreased NADPH-dependent redox signaling.28 The latter findings are consistent with the observation that when compared with whites, blacks have, in general, decreased vascular density in hypertrophied myocardium.

These data support the view that genetic polymorphisms and mutations that are more prevalent in specific ethnic populations may in part account for changes in vascular phenotype that contributes to the susceptibility to CVD. Understanding the interactions among these genetic variants and between these variants and environmental factors is essential for predicting accurately disease risk and therapeutic response in specific ethnic groups, as well as in the population at large.

Summary and Recommendations

Thoughtful attention to the complex tapestry of race and ethnicity is needed and essential for an accurate and complete understanding of the genetic basis for racial and ethnic disparities in CVD. An intrinsic conflict exists in the pursuit of genetic definitions of race. Cardiovascular investigators and practitioners must balance the risk of focusing on race (which may further entrench racism) against the potential for scientific discovery, wherein the use of race or ethnicity may unveil knowledge about the scientific basis of group disparities in CVD. We realize that the reductionistic focus of the biological basis of race ignores the complex and dynamic interactions among the social, geographic, and cultural forces that contribute to race and ethnicity. Ignoring race, however, may hamper scientific discoveries that could lead to a reduction in the disparities between racial or ethnic groups in regard to testing, diagnosis, and treatment of CVD.

Through its strategic initiatives, the AHA is uniquely positioned to provide leadership that improves the funding for the number of awards in both basic and population sciences and that increases funding for and efforts at training racial/ethnic minorities in the life and biomedical sciences. We urge
the AHA to pursue these initiatives, and make the following recommendations:

- Examine whether key polymorphisms believed to be responsible for CVD and its risk factors are enriched in certain racial/ethnic groups, and if such polymorphisms contribute significantly to racial/ethnic disparities in CVD risk.
- Study whether or not racial/ethnic disparities in polymorphisms can be used to guide prevention and treatment.
- Advocate against genetic, ethnic, and racial discrimination in insurance, health care, and employment.

References


Key Words: AHA Conference Proceedings • genetics • hypertension • nitric oxide • population
Discovering the Full Spectrum of Cardiovascular Disease: Minority Health Summit 2003: Report of the Basic Science Writing Group
Ivor J. Benjamin, Donna K. Arnett and Joseph Loscalzo

Circulation. 2005;111:e120-e123
doi: 10.1161/01.CIR.0000157741.99920.0C
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/111/10/e120

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/