

NEWS

Race and Medicine

Genetic studies of population differences, although controversial, promise clues to disease as well as new drug targets, scientists believe

Mention race and medicine in a group of scientists, and you are likely to provoke a range of heated opinions on whether it is useful, or even ethical, to consider how people of different ancestry respond to disease and treatments. No one disputes that some diseases strike disproportionately in some racial or ethnic groups—thalassemia in people whose ancestors came from the Mediterranean area, sickle cell anemia in people of African origins, for example. Less clear-cut than these single gene disorders—but the subject of increasing research—is the medical significance of a host of more subtle gene variants that appear in differing frequencies in various populations and that seem to influence a multitude of conditions.

So far, few candidate genes have been spotted, and the evidence is largely circumstantial. Some scientists dismiss the data as too preliminary, or the differences as insignificant. They worry that emphasizing biological differences in how people of different racial and ethnic groups respond to disease and treatments could unfairly stigmatize some patients and lead to inferior health care. Yet many scientists see exploration of differences among ancestral groups as a way to learn more about complex diseases and ultimately improve treatment for some groups of patients.

Already, drug companies are hunting for genetic reasons behind commonly observed medical differences between groups. Scientists are doing retrospective genetic analyses of data from drug trials. And 18 months ago a company called NitroMed launched a trial of a heart drug directed at compensating for what is believed to be a nitric oxide (NO) deficiency in many African Americans.

Everyone's ultimate dream is to have evidence on individual genotypes to guide medicine, a development that would make

racial identity biologically irrelevant. But that is decades away. Meanwhile, some scientists maintain that race can serve as a useful, if crude, indicator in sorting out why people experience diseases—and their treatments—differently and in finding new targets for drugs.

The argument

The chief argument against the notion that biological race can be medically meaningful is that there are far more genetic differences among individuals than there are between different ancestral groups. Neil Risch of Stanford University says that comparison is misleading, however. He

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Sabotaged by thrifty gene? Indians around the world have higher heart disease risk.

and others argue that if 30% of one population can't metabolize a certain drug, compared with 10% of another population, the between-group variability is low because most people in both groups lack this metabolism polymorphism. Nonetheless, this variation is significant when it comes to estimating the probability of response to treatment, he says. Geneticist

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Vulnerable. Cardiovascular disease is a particular scourge for African Americans.

David Goldstein of University College in London agrees: "If you say on average the difference between West Africans and Europeans is slight, that does not rule out a great many variants that influence how people respond to drugs."

Joel Buxbaum, who studies the molecular basis of disease at Scripps Research Institute in La Jolla, California, is persuaded as well. "A call to ignore [race] in diagnosis and treatment is a call to ignore biology," he says. "Research in the last 35 years has uncovered significant differences among racial and ethnic groups in their rate of drug metabolism, in clinical responses to drugs, and in drug side effects."

The most definitive evidence is on different levels of certain drug-metabolizing enzymes found in whites, blacks, and Asians. Some of these differences are quite dramatic; for example, Genaissance Pharmaceuticals in New Haven, Connecticut, has found a mutation of a major metabolism-controlling enzyme that occurs in 30% to 40% of Asians and less than 5% of members of other groups. Such findings help explain what many doctors have long observed—that many people of East Asian ancestry need smaller than average doses of a variety of heart, pain, and psychotropic drugs.

Less well documented—and more controversial—is emerging evidence on different patterns of cardiovascular disease among various populations. Researchers

are looking for biological roots not only of the well-known differences between blacks and whites, but also of another, much less publicized pattern of heart disease that disproportionately affects Asian Indians. Although neither of these groups seems more disease-prone in its ancestral environment, modern diets and lifestyles—particularly increased consumption of salt and fat, smoking, and inactivity—hit them hard. Even when investigators try to control for en-

environmental factors that could explain group differences, says cardiologist Clyde Yancy of the University of Texas Southwestern Medical Center in Dallas, “you can still see excess expression of disease.” Yancy and others see this as strong evidence for something genetic at work. But teasing it apart from other risk factors is proving daunting.

African-American risks

Blacks don't have more heart attacks than whites, but in the United States they die sooner from cardiovascular problems—both heart failure and strokes, says Yancy. They also have 10 times the rate of kidney failure, three times the incidence of cardiac hypertrophy, and more than twice the rate of diabetes, a destroyer of blood vessels. High blood pressure, which afflicts almost one-third of the U.S. black population, is the engine that, in large part, drives these related conditions. It leads to excess stress on organs, which respond with hypertrophy, or abnormal cell growth. Intertwined with the problem is a shortage of nitric oxide and, in many cases, excess salt sensitivity that in turn leads to fluid retention. Heart failure in blacks often occurs from damage to the left ventricle, which is responsible for sending freshly oxygenated blood through the body. Indeed, according to Yancy, in blacks, heart failure “may be a different disease with less favorable outcomes” than in whites.

Scientists are looking for genes that would explain these patterns, in particular for genes related to hypertension. Because NO, the chemical responsible for keeping blood vessels fit and toned, is important in the action of ACE (angiotensin-converting enzyme) inhibitors, genes for NO synthase, the enzyme most important for vascular NO production, are prime candidates. Dennis McNamara of the University of Pittsburgh Medical Center says the prevalence of certain versions of these genes is “much different in blacks and whites.” The variant that ACE inhibitors work best with is found in 60% of whites but only 30% of blacks, he says.

Also blood pressure-related is the gene for transforming growth factor- β (TGF- β). A group led by Phyllis August at Weill Medical College of Cornell University in New York City reported in 2000 that TGF- β 1 is overexpressed in black patients with end-stage renal disease or severe hypertension—and more so than in white patients with the same diseases. This looks like a promising genetic candidate for hypertension, the authors say, because TGF- β 1 regulates substances that act both as vasoconstrictors and as growth factors for vascular cells.

In addition to genes involved in high blood pressure, researchers have found a significant difference between blacks and

whites in genes that manipulate the response of the sympathetic nervous system to hormones like adrenaline. Stephen Liggett and colleagues at the University of Cincinnati reported last fall that possessing a combination of two particular versions of alpha and beta adrenergic receptors raised heart failure risk for blacks 10-fold. The high-risk version of the alpha receptor occurs almost exclusively in people of African origin and is present in about 40% of U.S. blacks, says Liggett. The researchers believe that depressed receptor function leads to excess release of norepinephrine, which is bad for the heart. The study is relevant for the use of beta-blockers, which inhibit the effects of adrenaline on beta receptors and which may be less effective in black heart patients. Liggett's team reported in the September issue of *Nature Medicine* that the high-risk beta receptor, which is also more common in blacks, raises the risk of heart failure in both mice and people and forebodes a poor response to beta-blockers.

Drug trials

Clinical trials have not been particularly helpful in illuminating such differences, says McNamara, because usually at least 80% of participants are white, and the pooling of data often obscures any racial differences.

That is why many researchers are particularly excited about the first clinical trial of a heart failure treatment that exclusively targets African Americans. It was launched in March 2001 by NitroMed, a company in Bedford, Massachusetts, to test a drug that may be uniquely beneficial to heart patients with NO deficiencies. The first-of-its-kind trial, called A-HeFT (for African-American Heart Failure Trial), is testing a drug called BiDil that was originally developed in the 1980s. BiDil combines vasodilators with an NO source and antioxidant properties to help potentiate treatment by ACE inhibitors. All patients in the trial will get standard medication; half will also get BiDil. Scientists believe that the trial, which has been endorsed by an array of groups, including the Association of Black Cardiologists Inc., should produce some definitive data on the

role of so-called NO subsensitivity in heart disease. McNamara, who calls the trial “very unique and very important,” says he and colleagues will do a genetic substudy, looking at a number of candidate markers for correlations with treatment response.

Researchers are also combing through data from earlier big heart trials. To get a fix on the nature of the suspected racial differ-

ence in response to beta-blockers, Buxbaum and colleagues are looking at data from BEST (the Beta-Blocker Evaluation of Survival Trial), which tested a nonselective beta-blocker called Bucindilol. In 2700 people with congestive heart failure, black patients as well as sicker ones generally failed to benefit from the drug. So the scientists are genotyping the 600 black patients to see if they can spot a genetic marker that will serve as a better indicator than race for whether the drug is likely to work. The results will be put in a DNA bank available for other investigators.

Although these studies are important, says Yancy, there is still no substitute for getting data from really big populations, not only to find vulnerability genes but to sort out what's “normal”—that is, genetic patterns (in any race or ancestral group) that do not predispose to heart disease. He has high hopes for another initiative, called UNITE-HF, led by the University of North Carolina with support from the drug company AstraZeneca, a U.K.-based company with U.S. headquarters in Wilmington, Delaware. UNITE-HF is collecting blood samples from the country's “stroke and heart attack belt” in the southern and southeastern United States. So far investigators have samples from some 800 ambulatory heart patients, both black and white, which they will analyze for the prevalence of suspect genes.

Indian hearts

The other population with a big heart disease problem is South Asian Indians. “Until 50 years ago it was hardly ever heard that Indians had high heart attack risk,” says cardiologist Prakash Deedwania of the University of California, San Francisco, Fresno, School of Medicine. But as more Indians are becoming westernized, many now have heart attacks as early as their mid-30s, and, he says, “the risk is enormously high all



NO booster. BiDil developer Jay Cohn.

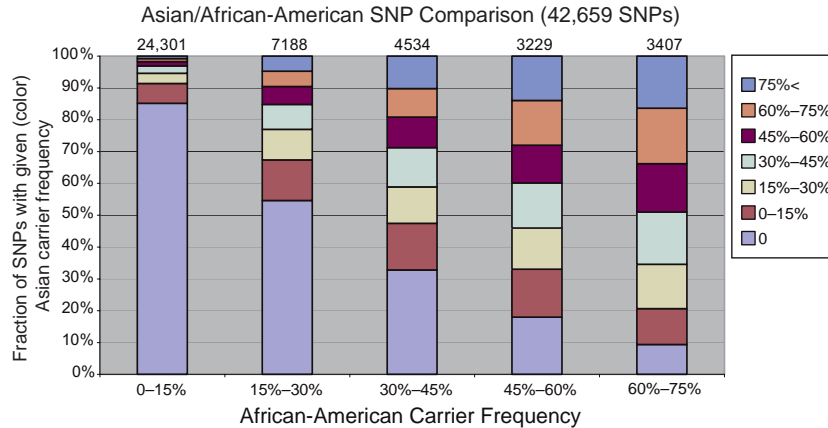
over the world.” A major risk factor is diabetes, which, according to figures collected by F. P. Cappuccio of St. George’s Hospital Medical School in London, is roughly four times as prevalent among Indians (in urban India and abroad) as in Londoners. Indians also tend to have high levels of triglycerides and low levels of HDL, the “good” cholesterol. One evolutionary explanation is the “thrifty gene hypothesis”: Over the millennia people in India endured cyclical famines; those who fared best were those who could conserve energy in abdominal fat. Now, for those exposed to plenty, this ability has turned into a disadvantage.

Some preliminary evidence for a genetic connection is emerging. Michael Miller, director of the Center for Preventive Cardiology at the University of Maryland Medical Center, says his group has found a high prevalence of an alteration in the apolipoprotein C3 gene, which regulates triglyceride metabolism, in Indians living in the United States. The researchers found this polymorphism by taking blood samples from 99 attendees at an Indian festival in Northern Virginia, as they describe in the January 2001 *American Journal of Cardiology*. This alteration is also associated with low HDL levels, says Miller, and possibly also insulin resistance. The group is now looking to see if people in India show the same pattern.

Investigators in New Delhi have already reported from a genetic analysis of 139 healthy males in Northern India that almost one-third carried a related variation in the apolipoprotein gene, a rare mutation in Caucasians. Furthermore, it was twice as frequent among those with elevated triglycerides—a risk factor for coronary artery disease.

More clues on how genetic variation could translate into different responses to medication should come from a new 6-week clinical trial, sponsored by AstraZeneca. It will compare Crestor (rosuvastatin), a new cholesterol-lowering drug that won government approval in August, with an older one (atorvastatin) in South Asian Americans. Deedwania says it will be the largest prospective trial ever done on Indians, with some 800 subjects from 150 centers around the country. Miller says Crestor may be better for Indians because it does a little better job at raising HDL.

Many Indian doctors believe that the Indian vulnerability to heart disease is striking enough to justify more preventive vigilance. Cardiologist Enas Enas, director of the Coronary Artery Disease in Indians Foundation in Lisle, Illinois, has stated that the goals of treatment for high blood pressure and obesity should be at least 10% lower, and cholesterol 20% lower, for Asian Indians than the goals recommended for Caucasians.



Biodiversity. More than 42,000 SNPs (genetic variations) found in African Americans are divided into columns according to how frequently they appear in that population. Colors indicate the frequency with which these same groups of SNPs are found in East Asians. For instance, in the second column, of the 7,188 SNPs that are found in 15% to 30% of African Americans, more than half show no variation in Asians.

Era of transition

Increasing awareness of possible genetic contributions to ethnic differences is reflected in a recommendation issued last January by the U.S. Food and Drug Administration (FDA). Calling for more scrutiny of subpopulations, FDA wants drug testers to use racial divisions specified by the Census Bureau “to ensure consistency in evaluating potential differences in drug response.”

Drugmakers are already on the lookout for genetic subgroups that could divulge new targets for therapeutic drugs. “I think we all believe there’s a lot of potential there,” says Gary Palmer, a Pfizer vice president in New York. Pfizer is particularly interested in hypertension-related genes in blacks and diabetes-related genes that could account for the high rates of the disease in both Asian Indians and Native Americans. AstraZeneca is also looking for population differences in drug response in its clinical trials. Spokesperson Gary Bruell says that if the company found that a drug has a “profound effect” on a particular group, it would label and promote it accordingly. “If a population doesn’t benefit, that could end up on the label too,” he adds.

Companies will probably be getting more help from outfits like Genaissance, set up 6 years ago to develop and market genet-

ic data. “Our company was founded on the principle that human genetic variation is critical to drug response,” says Claiborne Stephens, vice president for genetics. The obvious way to make a first cut at that variation, he notes, is to look at how evolution parceled out different versions of various genes according to the environments in which early human populations evolved.

One of its projects is a detailed data repository of more than 7,000 genes from 93 whites, blacks, and Asians, including information on the origins of their parents and grandparents, which companies can use as a reference in clinical trials. This is enough to give “a reasonable idea of what the gene frequencies are” in those groups, says Stephens (see chart).

Although everyone agrees that data are still preliminary, there’s been enough talk to get people concerned over how these findings could affect medical care. For example, Richard Cooper, a cardiologist at Loyola University Medical Center in Chicago, worries that any new information on race differences will lead to inferior care for non-whites. He says that so far, the best data on biological race differences are only “mixed,” and even where differences do exist they are never great enough to justify any race-based generalizations in the absence of genetic tests. He says there’s no evidence that risk factors don’t operate the same way for all groups. BiDil developer Jay Cohn of the University of Minnesota, Twin Cities, agrees that the best treatment is the same for any race. But he wouldn’t have a problem with, say, prescribing a drug that will boost NO in a black heart patient. If a doctor knows that a trait is “more common in one population than another,” that could be enough to “consider modifying one’s treatment strategy,” he says.

Although scientists hope that the advent of genomic medicine will obviate the need to grapple with race issues, Goldstein warns that the day of individually tailored treatments may be far away. Even after relevant genes are identified, it will be a chore to sort out what all the alleles do, he says. And so far, only a handful of such genes have been identified. “Pharmacogenetic studies are in their absolute infancy,” he says. So “the big question is the interim strategy: how to use ancestry now.”

—CONSTANCE HOLDEN

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