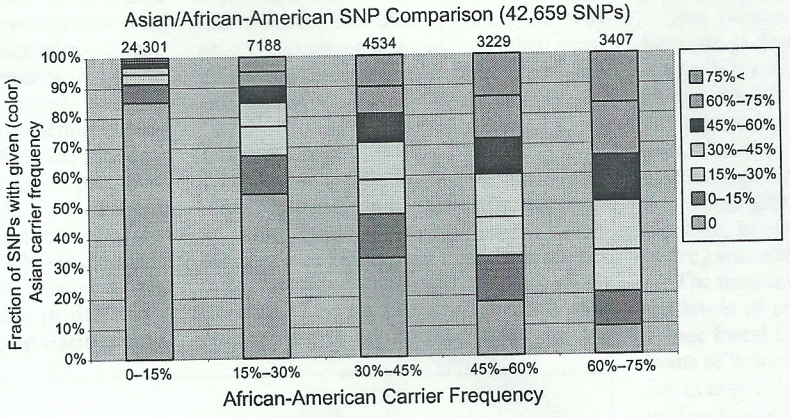
over the world." A major risk factor is diabetes, which, according to figures collected by F. P. Cappuccio of St. George's Hospital Medical School in London, is roughly four times as prevalent among Indians (in urban India and abroad) as in Londoners. Indians also tend to have high levels of triglycerides 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 7188 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 genetic 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 7000 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 nonwhites. 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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