Altered gene protects some African-Americans from coronary artery disease

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A team of scientists at Johns Hopkins and elsewhere has discovered that a single alteration in the genetic code of about a fourth of African-Americans helps protect them from coronary artery disease, the leading cause of death in Americans of all races.

Researchers found that a single DNA variation - having at least one so-called guanine nucleotide in a base pair instead of a combination without any guanine - on a gene already linked to higher risk of coronary disease in other races is linked in blacks to decreased risk. Specifically, the study showed that otherwise healthy African-American men and women with the alternative genetic code had a fivefold reduction in the likelihood that their arteries would narrow or clog.

For African-Americans who inherited two copies of the guanine gene variant, one from each parent, the risk reduction was even more dramatic. They were 10 times less likely to have coronary heart disease, which disproportionately afflicts a greater number of African-Americans than whites or any other ethnic group. Nearly 17 million Americans have an arterial problem plaguing the heart, causing a half-million deaths, annually.

"What we think we have here is the first confirmed hereditary link to cardiovascular disease among African-Americans and it is a protective one," says senior study investigator and health epidemiologist Diane Becker, M.P.H., Sc.D. "This newly found link in African-Americans was not only protective instead of harmful but was also found at a precise

location on gene CDKN2B, a gene close to the single base pair modification tied to other increased risk of coronary artery disease in other races."

Becker emphasizes that only an estimated quarter of blacks have the protective CDKN2B code, and only 6 percent have two copies, so "while a lot of African-Americans have this protective genetic modification, most do not." Advance testing for the genetic marker, she says, could ultimately in the future assist physicians in risk-stratifying those without inherited protection so they could be monitored more closely for early signs and symptoms of disease.

The findings are set to appear in the *Journal of Human Genetics* online Jan. 27.

Becker, a professor at both the Johns Hopkins University School of Medicine and Hopkins' Bloomberg School of Public Health, and a team that included researchers at Duke and Emory universities, also say their results, based on blood analysis from 548 black men and women in the Baltimore region and confirmed in several hundred more in the Atlanta and Durham, N.C., regions, help explain why earlier studies found potentially dangerous genetic connections to this type of heart disease in Caucasians, Hispanics and Asians, but failed to find a negative tie-in to the disease in blacks.

Earlier studies, says Becker, had involved genome-wide reviews in multiracial populations and taken "a needle in the haystack approach" to finding that one change in a string of some 58,000 base pairs, in a chromosomal region known as 9p21. That region, which includes CDKN2B, is associated with higher rates of coronary disease in non-blacks.

The team's latest analysis was successful, she believes, because it had a

large and sufficiently broadly based black volunteer population. The study group comprised men and women between the ages of 26 and 60. Investigators also focused on the 9p21 region and a subsection of genetic material within called ANRIL that overlaps and is closely held to CDKN2B, but away from the deleterious genetic variant found earlier.

Johns Hopkins cardiologist Brian Kral, M.D., M.P.H., says the abundance of activity in this particular region of the genome, including CDK2NB and ANRIL, suggests that everyday replication of this zone could play a more fundamental, underlying role in the progression of coronary artery disease in all races.

Kral, an assistant professor at Johns Hopkins and its Heart and Vascular Institute. was co-lead investigator of the latest study, along with Hopkins genetic epidemiologist Rasika Mathias, Sc.D. The team next plans to further investigate the ANRIL subregion of 9p21 to see if any single genetic changes speed up or slow down progression of coronary diseases.

Blood samples for the genetic analysis came from a larger study being led by Becker of some 4,000 people from white and African-American ethnic backgrounds. Called the Genetic Study of Atherosclerosis Risk (GeneSTAR), under way at Johns Hopkins since 1983, it involves participants who were all healthy upon enrollment, with no existing symptoms of heart disease. All were monitored for at least five years with periodic check-ups to see who developed heart disease and who did not. Each had a sibling or a parent who had a history of coronary artery disease or some other symptom of blocked arteries, such as chest pain or shortness of breath. The latest study was based on results collected through 2007, by which time 35 black study participants had suffered some form of heart attack or needed an angioplasty or X-ray scan of the heart's blood vessels to confirm or rule out arterial blockages.

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