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2 Altered Genes Are Linked To Congestive Heart Failure

By GINA KOLATA

People who inherit common variants of two genes have 10 times the risk of developing congestive heart failure, a condition that afflicts five million Americans, researchers say.

Congestive heart failure is a leading cause of death in the nation, but the researchers say their findings may help doctors identify drugs that are most likely to help patients and to find people at high risk early enough to arrest the disease.

In a paper published today in The New England Journal of Medicine, researchers at the University of Cincinnati proposed that the gene variants might predispose people to the disease.

The researchers looked at 159 patients with congestive heart failure, comparing them with 189 people who were similar in other respects, including race, but who did not have the disease. They discovered that their suspicions about the genes were correct.

Other experts said the results were among the first soundings of a new era in medicine in which doctors identify an individual's genetic variations to help him avoid illness.

The findings suggest that patients with the gene alterations might be helped by drugs that can impede the altered genes' effects, and they show how altered genes can amplify each other to cause disease.

One of the altered genes confers a fivefold increase in risk of heart failure. The other has no effect by itself but when combined with alterations in the first gene leads to a tenfold increase.

"It's fantastic," Dr. Arthur M. Feldman, chairman of the department of medicine at Jefferson Medical College in Philadelphia, said of the new findings. Dr. Feldman, who was not involved in the study, added, "This is the next era of care for heart failure patients."

Dr. Douglas Mann, a heart failure expert at the Houston Veterans Affairs Medical Center and Baylor College of Medicine who also was not involved in the study, called it "a substantial step forward."

People who do not have either genetic variation can still develop the disease. But the results may help explain why the condition is much more common in African-Americans than in Americans of European descent. About 5 percent of blacks in the general population have the altered two-gene combination while fewer than 1 percent of whites have it.

As for the gene variant that, by itself, increases risk fivefold, 17 percent of blacks in the general population have it while only 2 percent of whites do. The researchers did not determine the frequency of the gene variants in the population as a whole.

In congestive heart failure, the heart is unable to pump effectively. Patients' hearts grow large in an increasingly futile effort to accommodate, but as the organ continues to fail, fluid accumulates in the patients' lungs. The patients become so short of breath that they cannot walk across a room, and half die within five years.

More patients are hospitalized for congestive heart failure than for all cancers combined. While drugs can help, the condition remains difficult to treat. The only cure is a heart transplant for those still healthy enough to receive one and lucky enough to have a donor.

The new research, by Dr. Stephen B. Liggett, a molecular geneticist and heart failure specialist, and Dr. Lynne E. Wagoner, a heart failure and heart transplant expert, both at Cincinnati, and their colleagues, tried to determine whether particular genes might increase a person's risk.

Dr. Liggett knew that genes controlling the hormone norepinephrine make the heart pump more blood. Maybe, he reasoned, some people inherit versions of those genes that stimulate the heart too much. After decades of such overstimulation, the result might be heart failure.

One of the genes, an alpha-2 adrenergic receptor, controls the release of norepinephrine in the heart. The other, a beta-1 adrenergic

receptor, locks the norepinephrine onto heart muscle cells, making them contract.

Laboratory studies led Dr. Liggett to suspect that alterations in the genes might be important in heart failure. The altered alpha-2 receptor might flood heart cells with norepinephrine, and the altered beta-1 receptor might make the cells respond more forcefully to the hormone.

The gene combination, said Dr. Michael Bristow, a heart failure expert at the University of Colorado Health Science Center in Denver, "is like a double whammy to the failing heart." Drugs that tamp down the genes' activities might be most effective for these patients, he said.

Such drugs are already available. One group, alpha-2 agonists, suppress the activity of the first variant gene and another, beta-blockers, block the locking mechanism on the heart cells. Now, when doctors prescribe those drugs for heart-failure patients, only about half respond. The new study raises the possibility that the responders may be patients with the altered genes.

While that hypothesis must be tested, Dr. Bristow said, the data "strongly suggests" it.

Dr. Roger J. Hajjar, a cardiologist at Massachusetts General Hospital who wrote an editorial accompanying Dr. Liggett's paper, said he knew of several research papers, as yet unpublished, confirming its conclusions. "There's some very strong evidence that what they have unraveled is true," he said in an interview. "There's definitely a lot of excitement."

Dr. Liggett suggests it might make sense to offer genetic testing to relatives of heart-failure patients who have the altered genes.

"The absolute first take-home message is that we can identify early on people who are genetically programmed to have a higher risk of heart failure," he said. "The question is, What could you do about that? The most sensible thing would be to lower to zero all the other risk factors. High blood pressure -- you have to have perfect blood pressure control. Diabetes -- you can't have diabetes. Smoking -- absolutely not. High cholesterol -- absolutely not. Obesity and low physical activity -- you can't have that."

People with the altered genes might also have echocardiograms every year or two to see if their hearts are enlarging, a first sign of possible heart failure.

Dr. Liggett said he had not even told the patients in his study whether they had the genes. He is waiting for confirmation from a second study and would need the approval of his medical center's ethics board.