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Genetic Variation Found that Predicts Response to Heart Failure Medication

Discovery may open door to personal therapy for this deadly heart disease

DENVER (July 10, 2006) – Researchers at the University of Maryland School of Medicine in Baltimore and the University of Colorado School of Medicine in Denver have identified a common genetic variation that could help determine whether a person with heart failure would benefit from beta-blockers, a class of drugs used to treat chronic heart failure. The findings are significant because it often takes several months to determine if a specific beta blocker is working for a patient. Time is of the essence because one in five patients with heart failure will die within a year of diagnosis. The findings are published online this week in the *Proceedings of the National Academy of Sciences* (www.pnas.org).

In a study that compared an investigational beta-blocker to a placebo (or sugar pill), researchers found a 38 percent reduction in the death rate among patients who took the beta-blocker and who also had two copies of a genetic variant called arginine (Arg-389). In addition, these patients had a 34 percent reduction in another benchmark, the combined number of hospitalizations and deaths. People with another genetic variant, glycine (Gly-389), had no response to the drug compared to the placebo.

“For the first time, we have a genetic test that will help guide us to the best treatment for individual patients with heart failure and provide what has been called personal medicine,” says the study’s principal investigator, Stephen B. Liggett, M.D., professor of medicine and physiology at the University of Maryland School of Medicine and director of its cardiopulmonary genomics program. “This personalized therapy, based on genes, gives us an opportunity to tailor therapy in a way that we really were never able to do before.”

The genetic variance occurs in the beta-1 adrenergic receptor, which is the target for beta-blockers. People either have the Arg variant or the Gly variant. Dr. Liggett says the type of variant does not predispose a person to develop heart failure.

Beta-blockers reduce demand on the heart, slow the heart rate and prevent irregular heartbeat. They block receptors in the heart that normally respond to adrenalin and cause the heart to pump stronger. In heart failure, the heart’s impaired pumping function causes adrenalin to make the heart work harder. Beta-blockers allow the heart to get some relief from the overactive pumping, develop a normal cellular structure and shrink in size.

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Despite their usefulness, beta-blockers and other heart failure drugs present a treatment challenge, because their effect on a given patient is somewhat unpredictable. “It has been difficult to explain the variability of response to treatment, even among patients with similar ages and other characteristics. This is especially the case with beta-blockers, one of the cornerstones in the treatment of heart failure,” says Michael Bristow, M.D., Ph.D., a cardiologist at the University of Colorado School of Medicine and one of the study’s authors. “We hypothesized that the variability in response to beta-blockers was due to important functional genetic variation in the beta-1 receptor, and this indeed appears to be the case.”

The researchers’ conclusions are based in part on a retrospective look at data from a placebo-controlled study of the drug bucindolol, during which 1,040 heart failure patients were followed for up to four years. The study volunteers also consented to participate in a genetic sub-study which involved an analysis of their DNA, a process called genotyping. The researchers looked at four parameters: whether the patients had the real drug or the placebo, and whether they had the Arg-389 receptor or the Gly-389 receptor.

In addition, the researchers examined normal donor hearts as well as hearts removed from patients who were receiving heart transplants and discovered that, compared to Gly-389, hearts with two copies of the Arg gene had a greater response to an adrenaline-like compound called isoproterenol as well as bucindolol and several other drugs.

The researchers also looked at the genetic variants and the response to the beta blocker in black patients compared to whites, and found that genetics and not race determined who benefited best from the drug. “We believe it is inappropriate to use a race-based prescribing approach, because within any given ethnic or racial population there is a genetic variability with that group. Therefore, some people will have the response gene and some will not,” says Dr. Liggett.

Heart failure affects nearly 5 million Americans, according to the Heart Failure Society of America. Less than 50 percent of patients live past five years after their initial diagnosis and less than 25 percent are alive at 10 years. The risks of heart failure include high blood pressure, a prior heart attack, abnormal heart valves and diabetes. In addition, a large number of patients have a form of heart failure called idiopathic cardiomyopathy, where no predisposing factor can be identified.

Heart failure develops when the heart is not able to pump enough blood to meet the body’s needs. The heart compensates for this loss in pumping capacity by growing larger, increasing muscle mass and pumping faster to increase the heart’s output. These changes typically occur over a long period of time, masking the problem. Eventually, the heart and the body cannot keep up with the demands, and the person begins to experience the fatigue and breathing problems that often are the first signs of the disease.

Dr. Liggett says one of the main possibilities of the Human Genome Project and related efforts is the concept of tailoring therapy based on genetics, a field called pharmacogenetics. “It has not turned out to be so easy,” he says, “but this is one of the few examples that has come to fruition.”

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The study was funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health and the Department of Veterans Affairs Cooperative Studies Program.

Dr. Liggett is a consultant to ARCA Discovery of Denver. Dr. Bristow is an officer and equity holder in ARCA Discovery. The company is in the process of filing a new drug application with the Food and Drug Administration for bucindolol.

The University of Colorado School of Medicine faculty work to advance science and improve care as the physicians, educators and scientists at University of Colorado Hospital, The Children's Hospital, Denver Health, National Jewish Medical and Research Center and the Veterans Administration Medical Center. The School is part of the University of Colorado at Denver and Health Sciences Center, one of three campuses in the University of Colorado system. For more information, visit the Web site at www.uchsc.edu or the UCDHSC Newsroom at <http://www.uchsc.edu/news>.

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