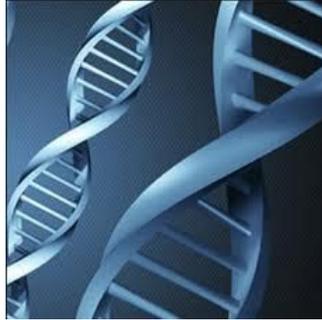


## Researchers Uncover New Gene For Heart Failure In Caucasians



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In addition to lifestyle factors, scientists have shown that heart failure has a strong heritable component, but identifying the responsible genes has been a major challenge. Now, new research has identified a common genetic risk factor for heart failure in Caucasians that is also linked to kidney function. The study, a collaboration between the University of Pennsylvania School of Medicine, Washington University School of Medicine, and other institutions, was published online in *The Proceedings of the National Academy of Sciences*.

"The big surprise is that our results point to a kidney gene, and not a heart gene," says Thomas P. Cappola, MD, ScM, assistant professor of Medicine at Penn and a lead author on the study. "It does make a lot of sense, however. When physicians treat heart failure, kidney function is a major concern, and many heart failure drugs affect the kidney directly. Our findings show that the heart and kidney should also be considered together in exploring genetic predisposition to heart failure."

Heart failure is very complex and this has often stymied research using traditional approaches. "Our study is a successful example of a newer model of biomedical research in which several laboratories and institutions combine numerous scientific approaches to tackle difficult research problems," said Cappola. For example, the research leveraged unique genotyping platforms (the IBC gene array) and study populations (the Penn Heart Failure Study and the Human Heart Tissue Bank) at the University of Pennsylvania. These resources were coupled with advanced sequencing approaches and laboratory models at Washington University.

"The results of this study highlight the advantage of performing unbiased studies to find DNA sequence variants associated with disease," said Gerald W. Dorn II, MD, professor of Medicine at Washington University School of Medicine and also a lead author on the study. "Nobody had previously considered that kidney-specific gene defects might predispose a person to heart failure."

The gene variant is common in Caucasians and changes the amino-acid sequence of CLCNKA, a kidney protein that controls chloride secretion in the urine. The change in CLCNKA substantially impairs its function. Similar but rare mutations in CLCNKA can cause striking elevation in renin and aldosterone, hormones which have been shown to increase heart failure risk.

The researchers say approximately one half of Caucasians have one copy of the variant CLCNKA gene, with an estimated 27 percent increase in heart failure risk, and one quarter carry two copies, with a 54 percent increase in risk. But they also caution the carrying the variant is not a definitive indicator of developing heart failure. Cappola says, "The more likely scenario is that heart failure risk associated with gene will only express itself if you have other cardiac problems. For example, if you have high blood pressure or heart attack, the chance of developing heart failure is more likely if you have also inherited the CLCNKA risk variant."

Cappola and Dorn plan on continuing their long-standing collaboration by studying what CLCNKA might mean in clinical practice. They have designed a heart failure prevention trial using readily available drugs that oppose the hormone aldosterone in CLCNKA carriers to be performed at University of Pennsylvania and at Washington University. If successful, these findings could open the door to tailored individual preventative therapy based on personal genotype, or "personalized medicine."

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