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## Genetic Mutation Causes Heart Failure

HHMI researchers have discovered a genetic mutation that damages heart muscle so that it dilates to the point where the heart can no longer pump blood.

The discovery may have immediate significance for millions of people affected by dilated cardiomyopathy, says senior investigator Mark Keating of the Howard Hughes Medical Institute at the University of Utah. Although there is typically a poor prognosis for patients with dilated cardiomyopathy, Keating says that his team's research suggests that damage may be mitigated by relaxing cardiac muscle with beta blockers, drugs commonly used for hypertension.

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**"It's a new way to think about heart failure."**

— **Mark T. Keating**

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"If we can help the heart to relax a bit before the damage is really serious, we might be able to reduce the rate of cell death and slow down the course of the disease," Keating said. Keating's team published their research in the May 1, 1998, issue of *Science*.

Most therapies for heart failure make the heart work harder to compensate for its inefficiency. This is just the opposite of what our data suggest should be done, Keating says. While a few cardiologists have successfully used beta blockers to treat heart failure, most have not tried using beta blockers because it is counter-intuitive, he notes. "It didn't make sense to use them before, but now it does," he says. "I hope this allows physicians to try beta blockers with conviction."

Keating and colleagues from the Mayo Clinic are the first to show that mutations in actin molecules are associated with a human disease. Actin is a ubiquitous structural protein found in cells in many types of organisms from rice to yeast to mammals. Humans have six genes that produce different forms of actin. One type of actin provides scaffold-like support for heart muscle cells and works with the protein myosin to generate the contractile force in muscle.

Researchers have suspected that genetic factors are responsible for some forms of heart failure, but it took a novel method of extracting genes from two unrelated families to identify the defect. This missense mutation? in which one amino acid in actin is substituted for another? reduced actin's ability to transmit contractile force in heart cells.

Keating likens the actin mutation to a hairline fracture in bone. "If you are just walking around with a hairline fracture of your leg bone, there will be some discomfort, but you will be okay. If you want to run the Boston Marathon, however, the increased stress of running will fracture the bone." Similarly, episodic stress on the heart can produce cracks in actin's structure that can eventually cause heart cells to die, which leads to dilated cardiomyopathy. "This damage is initially very subtle, but becomes important over time," Keating says.

Inherited and non-inherited forms of heart failure appear similar at the molecular level, which leads Keating to speculate that they share a common mechanism? damage to the actin scaffold. "It's a new way to think about heart failure."